12-05-07 07/929961 DAE 8

# IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 5,317,016 Issued: May 31, 1994
Expiration Date: August 14, 2012

Inventors: Yasuhiro Nishitani; Tadashi Irie; Yutaka Nishino
Title: PYRROLIDYLTHIOCARBAPENEM DERIVATIVE

**Mail Stop Patent Extension**
**Commissioner for Patents**
**P.O. Box 1450**
**Alexandria, Virginia 22313-1450**

## APPLICATION FOR EXTENSION OF PATENT TERM (37 C.F.R. § 1.740)

Pursuant to 35 U.S.C. §156(d) and 37 C.F.R. §1.740, Shionogi Seiyaku Kabushiki Kaisha ("Applicant") as Assignee and patent owner of the above-captioned patent, hereby petitions for extension of U.S. Patent No. 5,317,016 (the '016 Patent). In support of such Petition, Applicant provides the following information:

### I. SIGNATURE REQUIREMENTS (37 C.F.R. §1.730)

#### A. IDENTIFICATION OF PERSON(S) SUBMITTING THE APPLICATION

I, Thomas J. Dodd, represent that I am a registered practitioner appointed by the patent owner of record. A Power of Attorney, authorizing Thomas J. Dodd to act on behalf of the Patent Owner is attached hereto as **Exhibit 6**.

#### B. RECORDAL OF ASSIGNMENT IN PTO

This application USSN 07/929,061 filed August 14, 1992, claiming priority from Japanese patent application SN 3-207972, filed August 20, 1991, and Japanese patent application 4-35366, filed February 21, 1992. An assignment of U.S.S.N. 07/929,061 was recorded: Date: August 14, 1992 at Reel/Frame: 6224/0329 from the named inventors to Shionogi Seiyaku Kabushiki Kaisha.

## K. ACKNOWLEDGEMENT OF DUTY OF DISCLOSURE (1.740(a)(13))

I, Thomas J. Dodd, the person signing below, acknowledge the duty to disclose to the Director of the U.S. Patent and Trademark Office and to the Secretary of Health and Human Services any information that is material to the determination of entitlement to the extension being sought herein.

## L. FEE (1.740(a)(14))

The Application fee due is $1,120.00 (37 C.F.R. § 1.740(a)(14) and § 1.20(j).

Authorization is hereby made to charge the amount of $1,120.00 to Deposit Account No. 10-750.

Please also charge any additional fees required by this paper or credit any overpayment to Deposit Account No. ~~10-750~~ 10-0750.

## M. CORRESPONDENCE (1.740(a)(15))

Please direct all inquiries and correspondence relating to this application to:

Philip Johnson, Esq.
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08816

Attn: Thomas J. Dodd

Phone: (732) 524-2782
Facsimile: (732) 524-2134

## N. COPIES (1.740(a)(15)(b)) and MPEP 275

Four additional copies of this application are attached, making a total of five copies being submitted.

**Conclusion**

In conclusion, on the basis of the information provided herein, Applicant respectfully asserts that U.S. Patent No. 5,317,016 is entitled to the requested 1025 day extension of its term to June 5, 2015.

Prompt action on this application is respectfully requested.

Date: December 4, 2007

Reg. No.: 31,010
Tel. No.: 732-524-2782
Customer No.: 000027777

Thomas J. Dodd, Esq.
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08893
U.S.A.

*IN THE UNITED STATES PATENT AND TRADEMARK OFFICE*

Patent No.: 5,317,016

Issued: May 31, 1994
Expiration Date: August 14, 2012

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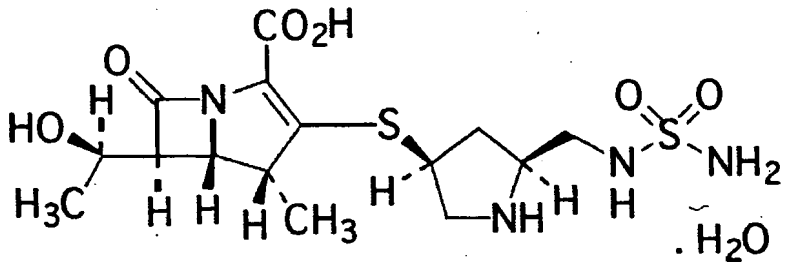
## II. APPLICATION REQUIREMENTS (37 C.F.R. §1.740)

### A. IDENTIFICATION OF APPROVED PRODUCT (1.740(a)(1))

The United States Food and Drug Administration ("FDA") has approved New Drug Application ("NDA") No. 22-106 for DORIBAX™ (doripenem). The active ingredient of DORIBAX is doripenem, which is contained in the drug product as doripenem monohydrate. A copy of the FDA Approval Letter and the approved labeling is attached hereto as **Exhibit 1**.

The chemical name for doripenem is (4R,5S,6S)-3-[((3S,5S)-5-[[(aminosulfonyl)amino]methyl]-3-pyrrolidinyl)thio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.

Doripenem (as doripenem monohydrate) has the following structural formula:




Each vial of DORIBAX contains doripenem monohydrate equivalent to 500 mg of doripenem (anhydrous).

### B. IDENTIFICATION OF THE FEDERAL STATUTE UNDER WHICH REGULATORY REVIEW OCCURRED (1.740(a)(2))

Regulatory review for this product occurred under the Federal Food Drug & Cosmetic Act ("FDC Act") §505(b), 21 U.S.C. §355 (new drugs).

### C. DATE OF APPROVAL (1.740(a)(3))

The FDA approved No. 22-106 for DORIBAX™ for commercial marketing or use under §505 of the FDC Act on October 12, 2007.

### D. IDENTIFICATION OF ACTIVE INGREDIENTS AND PREVIOUS APPROVAL INFORMATION (1.740(a)(4))

DORIBAX™ (doripenem) is a human drug product, the sole active ingredient of which is doripenem. Neither doripenem, nor any salt or ester thereof, has been previously approved, alone or in combination, for commercial marketing or use under the Food, Drug & Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

## E. TIMELY SUBMISSION OF APPLICATION (60 DAYS) (1.740(a)(5)

This application is being submitted within the sixty-day time period permitted for submission pursuant to 37 C.F.R. §1.720(f). The last date this application may be submitted is December 11, 2007.

## F. IDENTIFICATION OF PATENT (1.740(a)(6), (7), (8))

Name of the Inventors: Yasuhiro Nishitani; Tadashi Irie; Yutaka Nishino

Patent No. 5,317,016

Date of Issue: May 31, 1994

Date of Original Expiration: August 14, 2012

A copy of the patent, including the entire specification and claims (together with a copy of the certificate of correction of the '016 patent) is attached as **Exhibit 2**.

A copy of the U.S. Patent & Trademark Office Maintenance Fee Statements is attached as **Exhibit 3**.

No terminal disclaimer or reexamination certificate has been filed or issued in the '016 patent.

## G. IDENTIFICATION OF CLAIMS READING ON THE APPROVED PRODUCT (1.740(a)(9))

The '016 patent claims the active ingredient, a composition, and a method of using the approved product, which is doripenem. The claims directed to the approved product are 1-5 and 9-16. A complete claim chart that lists each applicable claim of the '016 patent and demonstrates the manner in which each applicable claim reads on the approved product is attached as **Exhibit 4**.

## H. RELEVANT DATES AND INFORMATION (1.740(a)(10))

The '016 Patent claims a human drug.

The effective date of the investigational new drug (IND) application was January 2, 2003, and the IND No. is 64,416.

The new drug application (NDA) was initially submitted on December 12, 2006 and was received by the FDA on December 12, 2006. The NDA Number is 22-106.

The NDA was approved on October 12, 2007.

## I. DESCRIPTION OF SIGNIFICANT ACTIVITIES OF APPLICANT DURING REGULATORY REVIEW (1.740(a)(11))

Attached as **Exhibit 5** is a "DESCRIPTION OF SIGNIFICANT ACTIVITIES OF APPLICANT DURING REGULATORY REVIEW" that provides a description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved Product and the significant dates applicable to such activities.

## J. STATEMENT THAT APPLICANT IS ELIGIBLE FOR EXTENSION (1.740(a)(12))

Attached as **Exhibit 7** is a "STATEMENT THAT APPLICANT IS ELIGIBLE FOR EXTENSION AND LENGTH OF EXTENSION CLAIMED" that states that in the opinion of the applicant the '016 Patent is eligible for the extension and the length of extension claimed, including how the length of extension was determined.

## K. ACKNOWLEDGEMENT OF DUTY OF DISCLOSURE (1.740(a)(13))

I, Thomas J. Dodd, the person signing below, acknowledge the duty to disclose to the Director of the U.S. Patent and Trademark Office and to the Secretary of Health and Human Services any information that is material to the determination of entitlement to the extension being sought herein.

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Facsimile: (732) 524-2134

## N. COPIES (1.740(a)(15)(b)) and MPEP 275

Four additional copies of this application are attached, making a total of five copies being submitted.

**Conclusion**

In conclusion, on the basis of the information provided herein, Applicant respectfully asserts that U.S. Patent No. 5,317,016 is entitled to the requested 1025 day extension of its term to June 5, 2015.

Prompt action on this application is respectfully requested.

Date: December 4, 2007

Reg. No.: 31,010
Tel. No.: 732-524-2782
Customer No.: 000027777

Thomas J. Dodd, Esq.
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08893
U.S.A.

Patent No. 5,317,016 Docket No. _____ By: TJD/va

Application of: Yasuhiro Nishitani; Tadashi Irie; Yutaka Nishino
Mailed: December 4, 2007

Entitled: PYRROLIDYLTHIOCARBAPENEM DERIVATIVE
**THE FOLLOWING HAS BEEN RECEIVED IN THE U.S. PATENT OFFICE ON THE DATES STAMPED HEREON:**

- ☐ Combined Declaration & POA
- ☐ Assignment
- ☐ Response
- ☐ Fee Transmittal
- ☐ Charge to Deposit Account 10-0750
- ☐ Amendment
- ☐ Extension of Time
- ☐ Issue Fee Transmittal
- ☐ PCT Filing _____
- ☐ IDS & Form 1449 _____
- ☒ Cert. of Mailing
- ☐ Drawings _____ sheets
- ☐ MPEP 609/_____
- ☐ Notice of Appeal
- ☐ Brief
- ☐ Priority Document
- ☐ Status Inquiry
- ☐ Sequence Listings/Diskette
- ☐ Biological Deposit Declaration
- ☐ Other Application for
- ☒ Other Extension of Patent Term (37 C.F.R. 1.740) & 4 copies

Exhibit 1 through Exhibit 7

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NEW BRUNSWICK NJ 08933-0002
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EMS

*PATENT*

*IN THE UNITED STATES PATENT AND TRADEMARK OFFICE*

Patent No.: 5,317,016 Issued: May 31, 1994
Expiration Date: August 14, 2012

Inventors: Yasuhiro Nishitani; Tadashe Irie; Yutaka Nishino

Title: PYRROLIDYLTHIOCARBAPENEM DERIVATIVE

Mail Stop: Patent Extension
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

## Express Mail Certificate

"Express Mail" mailing number: EV546121397US

Date of Deposit: **December 4, 2007**

I hereby certify that 5 copies of this complete Application For Extension of Patent Term, including:

| | | | |
|---|---|---|---|
| Application- | 8 pages | Exhibit 1- | 28 pages |
| Exhibit 2- | 39 pages | Exhibit 3- | 4 pages |
| Exhibit 4- | 2 pages | Exhibit 5- | 24 pages |
| Exhibit 6- | 6 pages | Exhibit 7- | 3 pages |

were deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Vivian Austin
(Typed or printed name of person mailing paper or fee)

Vivian Austin
(Signature of person mailing paper or fee)

**Exhibit 1**

**FDA Approval Letter and Approved Labeling for DORIBAX™ (doripenem)**

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-106

**NDA APPROVAL**

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Attention: Catherine Glamkowski
Associate Director, North American Regulatory Liaison
920 U.S. Highway 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Glamkowski:

Please refer to your new drug application (NDA) dated December 12, 2006, received December 13, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DORIBAX™ (doripenem for injection).

We acknowledge receipt of your submissions dated January 30, March 30, April 9, 11, 12 (2), May 17, 18, 30, June 4, 6, 22, July 3, 12, 27, August 9, 10 (2), 17, 24, 28, September 4 (3), 13, 18, and October 2 and 8.

This new drug application provides for the use of DORIBAX™ (doripenem for injection) for the treatment of complicated intra-abdominal (cIAI)) and complicated urinary tract (cUTI) infections caused by susceptible isolates of the designated microorganisms.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at *http://www.fda.gov/oc/datacouncil/spl.html* that is identical to the enclosed labeling (text for the package insert) dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 22-106."

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission **"Final Printed Carton and Container Labels for approved NDA 22-106."** Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies for ages 0 to18 years until October 12, 2012.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. These commitments are listed below.

1. Deferred pediatric studies under PREA for the treatment of cUTI in pediatric patients ages 0-18 years.

   Final Report Submission: October 12, 2012

2. Deferred pediatric studies under PREA for the treatment of cIAI in pediatric patients ages 0-18 years.

   Final Report Submission: October 12, 2012

Submit final study reports to this NDA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitments must be clearly designated **"Required Pediatric Study Commitments"**.

We remind you of your postmarketing study commitments in your submission dated October 11, 2007. These commitments are listed below.

3. Conduct post-marketing surveillance study (such as a patient registry) regarding hemolytic anemia, renal failure/renal impairment, and seizures in doripenem-treated subjects.

   | | |
   |---|---|
   | Protocol Submission: | by June, 2008 |
   | Study Start: | by March, 2008 |
   | Final Report Submission: | by December, 2012 |

4. Conduct a Phase 1 study to assess potential interactions between doripenem and valproic acid.

   | | |
   |---|---|
   | Protocol Submission: | by December, 2007 |
   | Study Start: | by March, 2008 |
   | Final Report Submission: | by December, 2008 |

5. Conduct US surveillance studies for two years from the date of marketing DORIBAX to determine if resistance to doripenem has developed in those organisms specific to the indications in the label for complicated urinary tract infection and complicated intra-abdominal infection. The US surveillance studies on *Klebsiella pneumoniae* isolates should include monitoring for the presence of the KPC carbapenemase.

| | |
|---|---|
| Protocol Submission: | by December, 2007 |
| Study Start: | Ongoing |
| Final Report Submission: | by March, 2010 |

6. Conduct studies to define the mechanism(s) of resistance for isolates identified as being resistant to doripenem during the surveillance period (two years from the date of marketing).

| | |
|---|---|
| Protocol Submission: | Not applicable |
| Study Start: | by March, 2008 |
| Final Report Submission: | by March, 2010 |

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled **"Postmarketing Study Commitment Protocol", "Postmarketing Study Commitment Final Report", or "Postmarketing Study Commitment Correspondence."**

NDA 22-106 was not referred to an advisory committee for review for the following reasons: There are three previously approved antimicrobial agents in the carbapenem class. Evaluation of the safety data did not reveal particular safety issues that were unexpected for the carbapenem class, and the design and results of the efficacy trials did not pose particular concerns. Doripenem is an intravenous agent studied for more serious infections for which there is adequate justification for using an active controlled study designed to show non-inferiority.

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of

promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

In addition, we request that you submit one copy of the introductory promotional materials you propose to use for this product to this division.

Please submit one market package of the drug product when it is available.

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
HFD-001, Suite 5100
5515 Security Lane
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

**MEDWATCH-TO-MANUFACTURER PROGRAM**

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Susmita Samanta, MD, Regulatory Project Manager, at (301) 796-1400.

Sincerely,

*{See appended electronic signature page}*

Edward Cox, MD, MPH
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DORIBAX™ safely and effectively. See full prescribing information for DORIBAX™.

**DORIBAX™ (doripenem for injection) for Intravenous Infusion**
**Initial U.S. Approval: 2007**

To reduce the development of drug-resistant bacteria and maintain the effectiveness of DORIBAX™ and other antibacterial drugs, DORIBAX™ should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

### INDICATIONS AND USAGE

DORIBAX™ is a penem antibacterial indicated in the treatment of the following infections caused by designated susceptible bacteria:

- Complicated intra-abdominal infections (1.1)
- Complicated urinary tract infections, including pyelonephritis (1.2)

### DOSAGE AND ADMINISTRATION

- 500 mg every 8 hours by intravenous infusion administered over one hour for patients ≥18 years of age. (2.1)
- Dosage in patients with impaired renal function (2.2):

| CrCl (mL/min) | Recommended Dose of DORIBAX™ |
|---|---|
| > 50 | No dosage adjustment necessary |
| ≥ 30 to ≤ 50 | 250 mg IV (over 1 hour) every 8 hours |
| > 10 to < 30 | 250 mg IV (over 1 hour) every 12 hours |

### DOSAGE FORMS AND STRENGTHS

500 mg single-use vial (3)

### CONTRAINDICATIONS

Patients with known serious hypersensitivity to doripenem or to other drugs in the same class or patients who have demonstrated anaphylactic reactions to beta-lactams (4)

### WARNINGS AND PRECAUTIONS

- Serious hypersensitivity (anaphylactic) reactions have been reported with carbapenems and other beta-lactams (5.1)
- Loss of seizure control due to lower serum valproic acid levels may result from interaction with sodium valproate (5.2)
- *Clostridium difficile*-associated diarrhea (ranging from mild diarrhea to fatal colitis): Evaluate if diarrhea occurs (5.3)

### ADVERSE REACTIONS

Most common adverse reactions (≥ 5%) are headache, nausea, diarrhea, rash and phlebitis.

**To report SUSPECTED ADVERSE REACTIONS, contact Ortho-McNeil Pharmaceutical, Inc. at 1-800-526-7736 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.**

### DRUG INTERACTIONS

| Interacting Drug | Interaction |
|---|---|
| Valproic acid | Carbapenems may reduce serum valproic acid levels (7.1) |
| Probenecid | Reduces renal clearance of doripenem, resulting in increased doripenem concentrations (7.2, 12.3) |
| Drugs metabolized by cytochrome P450 enzymes | Doripenem neither inhibits nor induces major cytochrome P450 enzymes (12.3) |

### USE IN SPECIFIC POPULATIONS

- Dosage adjustment is required in patients with moderately or severely impaired renal function (2.2, 12.3)
- DORIBAX™ has not been studied in pediatric patients. (8.4)

**See 17 for PATIENT COUNSELING INFORMATION**

**Revised: 10/2007**

## FULL PRESCRIBING INFORMATION: CONTENTS*



*Sections or subsections omitted from the full prescribing information are not listed

## 1 INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of DORIBAX™ and other antibacterial drugs, DORIBAX™ should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting and modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

### 1.1 Complicated Intra-Abdominal Infections

DORIBAX™ (doripenem for injection) is indicated as a single agent for the treatment of complicated intra-abdominal infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Bacteroides caccae*, *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Streptococcus intermedius*, *Streptococcus constellatus* and *Peptostreptococcus micros*.

### 1.2 Complicated Urinary Tract Infections, Including Pyelonephritis

DORIBAX™ (doripenem for injection) is indicated as a single agent for the treatment of complicated urinary tract infections, including pyelonephritis caused by *Escherichia coli* including cases with concurrent bacteremia, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Dosage

The recommended dosage of DORIBAX™ is 500 mg administered every 8 hours by intravenous infusion over one hour in patients ≥18 years of age. The recommended dosage and administration by infection is described in Table 1:

**Table 1: Dosage of DORIBAX™ by Infection**

| Infection | Dosage | Frequency | Infusion Time (hours) | Duration |
|---|---|---|---|---|
| Complicated intra-abdominal infection | 500 mg | q8h | 1 | 5-14 days* |
| Complicated UTI, including pyelonephritis | 500 mg | q8h | 1 | 10 days*§ |

* Duration includes a possible switch to an appropriate oral therapy, after at least 3 days of parenteral therapy, once clinical improvement has been demonstrated.

§ Duration can be extended up to 14 days for patients with concurrent bacteremia.

## 2.2 Patients with Renal Impairment

Table 2: Dosage of DORIBAX™ in Patients with Renal Impairment

| Estimated CrCl (mL/min) | Recommended Dosage Regimen of DORIBAX™ |
|---|---|
| > 50 | No dosage adjustment necessary |
| ≥ 30 to ≤ 50 | 250 mg intravenously (over 1 hour) every 8 hours |
| > 10 to < 30 | 250 mg intravenously (over 1 hour) every 12 hours |

The following formula may be used to estimate CrCl. The serum creatinine used in the formula should represent a steady state of renal function.

$$\text{Males: Creatinine clearance (mL/min)} = \frac{\text{weight (kg)} \times (140 - \text{age in years})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females: Creatinine clearance (mL/min) = 0.85 x value calculated for males

DORIBAX™ is hemodialyzable; however, there is insufficient information to make dose adjustment recommendations in patients on hemodialysis.

## 2.3 Preparation of Solutions

DORIBAX™ does not contain a bacteriostatic preservative. Aseptic technique must be followed in preparation of the infusion solution.

Preparation of 500 mg dose:

- Constitute the vial with 10 mL of sterile water for injection or 0.9% sodium chloride injection (normal saline) and gently shake to form a suspension. The resultant concentration is 50 mg/mL. **CAUTION: THE CONSTITUTED SUSPENSION IS NOT FOR DIRECT INJECTION.**
- Withdraw the suspension using a syringe with a 21 gauge needle and add it to an infusion bag containing 100 mL of normal saline or 5% dextrose; gently shake until clear. The final infusion solution concentration is 4.5 mg/mL.

Preparation of 250 mg dose for patients with moderate or severe renal impairment:

- Constitute the vial with 10 mL of sterile water for injection or 0.9% sodium chloride injection (normal saline) and gently shake to form a suspension. The resultant concentration is 50 mg/mL. **CAUTION: THE CONSTITUTED SUSPENSION IS NOT FOR DIRECT INJECTION.**

- Withdraw the suspension using a syringe with a 21 gauge needle and add it to an infusion bag containing 100 mL of normal saline or 5% dextrose; gently shake until clear. Remove 55 mL of this solution from the bag and discard. Infuse the remaining solution, which contains 250 mg (4.5 mg/mL).

To prepare DORIBAX infusions in Baxter Minibag Plus™ infusion bags consult the infusion bag manufacturer's instructions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to use whenever solution and container permit. DORIBAX infusions range from clear, colorless solutions to solutions that are clear and slightly yellow. Variations in color within this range do not affect the potency of the product.

### 2.4 Compatibility

The compatibility of DORIBAX™ with other drugs has not been established. DORIBAX™ should not be mixed with or physically added to solutions containing other drugs.

### 2.5 Storage of Constituted Solutions

Upon constitution with sterile water for injection or 0.9% sodium chloride (normal saline) injection, DORIBAX suspension in the vial may be held for 1-hour prior to transfer and dilution in the infusion bag.

Following dilution of the suspension with normal saline or 5% dextrose, DORIBAX infusions stored at controlled room temperature or under refrigeration should be completed according to the times in Table 3.

Table 3: Storage and Stability Times of Infusion Solutions Prepared in Normal Saline or 5% Dextrose

| Infusion prepared in | Stability Time at Room Temp. (includes room temperature storage and infusion time) | Stability time at 2-8°C (Refrigeration) (includes refrigerator storage and infusion time) |
|---|---|---|
| Normal saline | 8 hours | 24 hours |
| 5% Dextrose | 4 hours | 24 hours |

Constituted DORIBAX suspension or DORIBAX infusion should not be frozen. This storage information applies also to DORIBAX™ diluted in Baxter Minibag Plus™.

## 3 DOSAGE FORMS AND STRENGTHS

Single use clear glass vials containing 500 mg (on an anhydrous basis) of sterile doripenem powder.

## 4 CONTRAINDICATIONS

DORIBAX™ is contraindicated in patients with known serious hypersensitivity to doripenem or to other drugs in the same class or in patients who have demonstrated anaphylactic reactions to beta-lactams.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) and serious skin reactions have been reported in patients receiving beta-lactam antibiotics. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. Before therapy with DORIBAX™ is instituted, careful inquiry should be made to determine whether the patient has had a previous hypersensitivity reaction to other carbapenems, cephalosporins, penicillins or other allergens. If this product is to be given to a penicillin- or other beta-lactam-allergic patient, caution should be exercised because cross-hyperreactivity among beta-lactam antibiotics has been clearly documented.

If an allergic reaction to DORIBAX™ occurs, discontinue the drug. Serious acute hypersensitivity (anaphylactic) reactions require emergency treatment with epinephrine and other emergency measures, including oxygen, IV fluids, IV antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated.

### 5.2 Interaction with Sodium Valproate

Carbapenems may reduce serum valproic acid concentrations to subtherapeutic levels, resulting in loss of seizure control. Serum valproic acid concentrations should be monitored frequently after initiating carbapenem therapy. Alternative antibacterial or anticonvulsant therapy should be

considered if serum valproic acid concentrations cannot be maintained in the therapeutic range or seizures occur. [see *Drug Interactions (7.1)*]

### 5.3 *Clostridium difficile*-Associated Diarrhea

*Clostridium difficile*-associated diarrhea (CDAD) has been reported with nearly all antibacterial agents and may range in severity from mild diarrhea to fatal colitis.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *C. difficile*.

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated. [see *Adverse Reactions (6.1)*]

### 5.4 Development of Drug-Resistant Bacteria

Prescribing DORIBAX™ in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

### 5.5 Pneumonitis with Inhalational Use

When DORIBAX™ has been used investigationally via inhalation, pneumonitis has occurred. DORIBAX™ should not be administered by this route.

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of labeling:

- Anaphylaxis and serious hypersensitivity reactions [see *Warnings and Precautions (5.1)*]
- Interaction with sodium valproate [see *Warnings and Precautions (5.2)* and *Drug Interactions (7.1)*]
- *Clostridium difficile*-associated diarrhea [see *Warnings and Precautions (5.3)*]

- Development of drug-resistant bacteria [see *Warnings and Precautions (5.4)*]
- Pneumonitis with inhalational use [see *Warnings and Precautions (5.5)*]

## 6.1 Adverse Reactions from Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be compared directly to rates from clinical trials of another drug and may not reflect rates observed in practice.

During clinical investigations, 853 adult patients were treated with DORIBAX™ IV (500 mg administered over 1 hour q8h) in the three comparative phase 3 clinical studies; in some patients, parenteral therapy was followed by a switch to an oral antimicrobial. [see *Clinical Studies (14)*] The median age of patients treated with DORIBAX™ was 54 years (range 18-90) in the comparative cUTI study and 46 years (range 18-94) in the pooled comparative cIAI studies. There was a female predominance (62%) in the comparative cUTI study and a male predominance (63%) in the pooled cIAI studies. The patients treated with DORIBAX™ were predominantly Caucasian (77%) in the three pooled phase 3 studies.

The most common adverse reactions (≥ 5%) observed in the DORIBAX™ phase 3 clinical trials were headache, nausea, diarrhea, rash and phlebitis. During clinical trials, adverse drug reactions that led to DORIBAX™ discontinuation were nausea (0.2%), vulvomycotic infection (0.1%) and rash (0.1%).

Adverse reactions due to DORIBAX™ 500 mg q8h that occurred at a rate ≥ 1 % in either indication are listed in Table 4. Hypersensitivity reactions related to intravenous study drug and *C. difficile* colitis occurred at a rate of less than 1% in the three controlled phase 3 clinical trials.

**Table 4:** **Adverse Reactions† with Incidence Rates (%) of ≥1% and Adverse Events†† Having Clinically Important Differences in Frequency by Indication in the Three Controlled, Comparative DORIBAX™ Phase 3 Clinical Trials**

| | Complicated Urinary Tract Infections (one trial) | | Complicated Intra-Abdominal Infections (two trials) | |
|---|---|---|---|---|
| System organ class | DORIBAX™ 500 mg q8h (n =376 ) | Levofloxacin 250 mg IV q24h (n = 372) | DORIBAX™ 500 mg q8h (n = 477) | Meropenem 1 g q8h (n = 469) |
| **Nervous system disorders** | | | | |
| Headache | 16 | 15 | 4 | 5 |
| **Vascular disorders** | | | | |
| Phlebitis | 4 | 4 | 8 | 6 |
| **Gastro-intestinal disorders** | | | | |
| Nausea | 4 | 6 | 12 | 9 |
| Diarrhea | 6 | 10 | 11 | 11 |
| **Blood and Lymphatic System Disorders** | | | | |
| Anemia†† | 2 | 1 | 10 | 5 |
| **Renal and Urinary Disorders** | | | | |
| Renal impairment/Renal failure†† | <1 | 0 | 1 | <1 |
| **Skin and subcutaneous disorders** | | | | |
| Pruritus | <1 | 1 | 3 | 2 |
| Rash* | 1 | 1 | 5 | 2 |
| **Investigations** | | | | |
| Hepatic enzyme elevation** | 2 | 3 | 1 | 3 |
| **Infection and Infestations** | | | | |
| Oral candidiasis | 1 | 0 | 1 | 2 |
| Vulvomycotic infection | 2 | 1 | 1 | <1 |

*includes reactions reported as allergic and bullous dermatitis, erythema, macular/papular eruptions, urticaria and erythema multiforme

**includes reactions reported as alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, and transaminases increased

† An adverse drug reaction was defined as an undesirable effect, reasonably associated with the use of DORIBAX™ that may occur as part of its pharmacological action or may be unpredictable in its occurrence.

†† An adverse event refers to any untoward medical event associated with the use of the drug in humans, whether or not considered drug-related.

### 6.2 Postmarketing Experience

The following adverse reaction has been identified during post-approval use of doripenem outside of the U.S. Because this reaction was reported voluntarily from a population of uncertain size, it is not possible to reliably estimate its frequency or establish a causal relationship to drug exposure.

Anaphylaxis

The following treatment-emergent adverse events (known to occur with beta-lactams including carbapenems) have been reported voluntarily during post-approval use of DORIBAX™ outside of the U.S. They are included due to their seriousness, although it is not possible to estimate their frequency and causality has not been established:

Stevens Johnson Syndrome
Toxic epidermal necrolysis
Interstitial pneumonia
Seizure

## 7 DRUG INTERACTIONS

### 7.1 Valproic Acid

A clinically significant reduction in serum valproic acid concentrations has been reported in patients receiving carbapenem antibiotics and may result in loss of seizure control. Although the mechanism of this interaction is not fully understood, data from *in vitro* and animal studies suggest that carbapenem antibiotics may inhibit valproic acid glucuronide hydrolysis. Serum valproic acid concentrations should be monitored frequently after initiating carbapenem therapy. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid concentrations cannot be maintained in the therapeutic range or a seizure occurs. [see *Warnings and Precautions (5.2)*]

### 7.2 Probenecid

Probenecid interferes with the active tubular secretion of doripenem, resulting in increased plasma concentrations of doripenem. [see *Clinical Pharmacology (12.3)*] Coadministration of probenecid with DORIBAX™ is not recommended.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

**Category B:** Doripenem was not teratogenic and did not produce effects on ossification, developmental delays or fetal weight following intravenous administration during organogenesis at doses as high as 1 g/kg/day in rats and 50 mg/kg/day in rabbits (based on AUC, at least 2.4 and 0.8 times the exposure to humans dosed at 500 mg q8h, respectively). There are no adequate

and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

### 8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DORIBAX™ is administered to a nursing woman.

### 8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

### 8.5 Geriatric Use

Of the total number of subjects in clinical studies of DORIBAX™, 28% were 65 and over, while 12% were 75 and over. Clinical cure rates in complicated intra-abdominal and complicated urinary tract infections were slightly lower in patients ≥ 65 years of age and also in the subgroup of patients ≥ 75 years of age versus patients < 65. These results were similar between doripenem and comparator treatment groups.

No overall differences in safety were observed between older and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Elderly subjects had greater doripenem exposure relative to non-elderly subjects; however, this increase in exposure was mainly attributed to age-related changes in renal function. [see *Clinical Pharmacology (12.3)*]

This drug is known to be excreted substantially by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function or pre-renal azotemia. Because elderly patients are more likely to have decreased renal function or pre-renal azotemia, care should be taken in dose selection, and it may be useful to monitor renal function.

### 8.6 Patients with Renal Impairment

Dosage adjustment is required in patients with moderately or severely impaired renal function. [see *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)*] In such patients, renal function should be monitored.

## 10 OVERDOSAGE

In the event of overdose, DORIBAX™ should be discontinued and general supportive treatment given.

Doripenem can be removed by hemodialysis. In subjects with end-stage renal disease administered DORIBAX™ 500 mg, the mean total recovery of doripenem and doripenem-M1 in

the dialysate following a 4-hour hemodialysis session was 259 mg (52% of the dose). However, no information is available on the use of hemodialysis to treat overdosage. [see *Clinical Pharmacology (12.3)*]

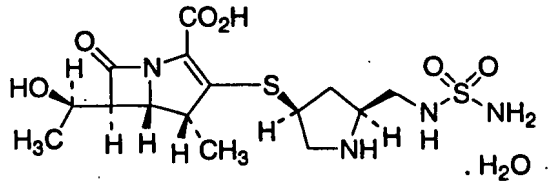
## 11 DESCRIPTION

DORIBAX™, doripenem monohydrate for injection vials contain 500 mg of doripenem on an anhydrous basis, a white to slightly-yellowish off-white sterile crystalline powder. All references to doripenem activity are expressed in terms of the active doripenem moiety. The powder is constituted for intravenous infusion. The pH of the infusion solution is between 4.5 and 5.5.

DORIBAX™ is not formulated with any inactive ingredients.

DORIBAX™ (doripenem monohydrate) is a synthetic broad-spectrum carbapenem antibiotic structurally related to beta-lactam antibiotics. The chemical name for doripenem monohydrate is (4*R*,5*S*,6*S*)-3-[((3*S*,5*S*)-5-[[(aminosulfonyl)amino]methyl]-3-pyrrolidinyl)thio]-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate.

Its molecular weight is 438.52, and its chemical structure is:




## 12 CLINICAL PHARMACOLOGY

Doripenem is a carbapenem with *in vitro* antibacterial activity against aerobic and anaerobic Gram-positive and Gram-negative bacteria.

### 12.1 Mechanism of Action

Doripenem is an antibacterial drug. [see *Clinical Pharmacology (12.4)*]

### 12.2 Pharmacodynamics

Similar to other beta-lactam antimicrobial agents, the time that unbound plasma concentration of doripenem exceeds the MIC of the infecting organism has been shown to best correlate with efficacy in animal models of infection. However, the pharmacokinetic/pharmacodynamic relationship for doripenem has not been evaluated in patients.

In a randomized, positive- and placebo-controlled crossover QT study, 60 healthy subjects were administered DORIBAX™ 500 mg IV every 8 hours x 4 doses and DORIBAX™ 1g IV every 8 hours x 4 doses, placebo, and a single oral dose of positive control. At both the 500 mg and 1g

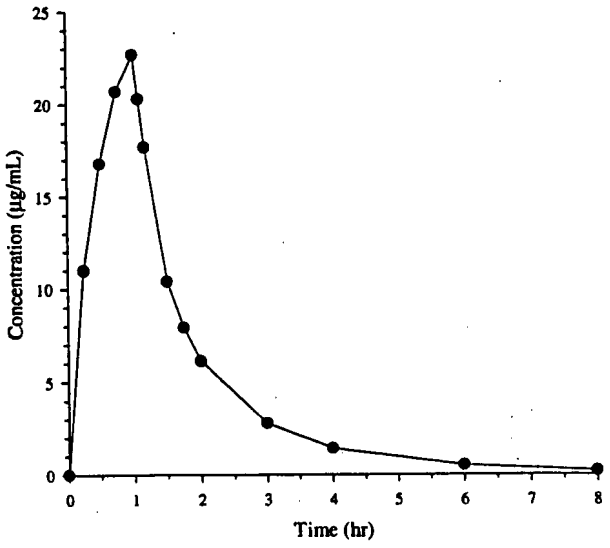
DORIBAX™ doses, no significant effect on QTc interval was detected at peak plasma concentration or at any other time.

## 12.3 Pharmacokinetics

- **Plasma Concentrations**

Mean plasma concentrations of doripenem following a single 1-hour intravenous infusion of a 500 mg dose of DORIBAX™ to 24 healthy subjects are shown below in Figure 1. The mean (SD) plasma $C_{max}$ and $AUC_{0-\infty}$ values were 23.0 (6.6) µg/mL and 36.3 (8.8) µg•hr/mL, respectively.

**Figure 1. Average Doripenem Plasma Concentrations Versus Time Following a Single 1-Hour Intravenous Infusion of DORIBAX™ 500 mg in Healthy Subjects (N=24)**




The pharmacokinetics of doripenem ($C_{max}$ and AUC) are linear over a dose range of 500 mg to 1g when intravenously infused over 1 hour. There is no accumulation of doripenem following multiple intravenous infusions of either 500 mg or 1g administered every 8 hours for 7 to 10 days in subjects with normal renal function.

- **Distribution**

The average binding of doripenem to plasma proteins is approximately 8.1% and is independent of plasma drug concentrations. The median (range) volume of distribution at steady state in healthy subjects is 16.8 L (8.09-55.5 L), similar to extracellular fluid volume (18.2 L).

Doripenem penetrates into several body fluids and tissues, including those at the site of infection for the approved indications. Doripenem concentrations in peritoneal and retroperitoneal fluid either match or exceed those required to inhibit most susceptible bacteria; however, the clinical

relevance of this finding has not been established. Concentrations achieved in selected tissues and fluids following administration of DORIBAX™ are shown in Table 5:

**Table 5: Doripenem Concentrations in Selected Tissues and Fluids**

| Tissue or Fluid | Dose (mg) | Infusion Duration (h) | Number of Samples or Subjects[a] | Sampling Period[b] | Concentration Range (μg/mL or μg/g) | Tissue- or Fluid-To-Plasma Concentration Ratio (%) Mean (Range) |
|---|---|---|---|---|---|---|
| Retroperitoneal fluid | 250 | 0.5 | 9[c] | 30-90 min[d] | 3.15-52.4 | Range: 4.1(0.5-9.7) at 0.25 h to 990 (173-2609) at 2.5 h |
| | 500 | 0.5 | 4[c] | 90 min[d] | 9.53-13.9 | Range: 3.3 (0.0-8.1) at 0.25 h to 516 (311-842) at 6.5 h |
| Peritoneal exudate | 250 | 0.5 | 5[c] | 30-150 min[d] | 2.36-5.17 | Range: 19.7 (0.00-47.3) at 0.5 h to 160 (32.2-322) at 4.5 h |
| Gallbladder | 250 | 0.5 | 10 | 20-215 min | BQL-1.87[e] | 8.02 (0.00-44.4) |
| Bile | 250 | 0.5 | 10 | 20-215 min | BQL-15.4[f] | 117 (0.00-611) |
| Urine | 500 | 1 | 110 | 0-4 hr | 601 (BQL[f]-3360)[g] | --- |
| | 500 | 1 | 110 | 4-8 hr | 49.7 (BQL[f]-635)[g] | --- |

[a] Unless stated otherwise, only one sample was collected per subject; [b] Time from start of infusion; [c] Serial samples were collected; maximum concentrations reported; [d] $t_{max}$ range ; [e] BQL (Below Quantifiable Limits) in 6 subjects; [f] BQL in 1 subject; [g] Median (range)

- **Metabolism**

Metabolism of doripenem to a microbiologically inactive ring-opened metabolite (doripenem-M1) occurs primarily via dehydropeptidase-I. The mean (SD) plasma doripenem-M1-to-doripenem AUC ratio following single 500 mg and 1 g doses in healthy subjects is 18% (7.2%).

In pooled human liver microsomes, no *in vitro* metabolism of doripenem could be detected, indicating that doripenem is not a substrate for hepatic CYP450 enzymes.

- **Excretion**

Doripenem is primarily eliminated unchanged by the kidneys. The mean plasma terminal elimination half-life of doripenem in healthy non-elderly adults is approximately 1 hour and mean (SD) plasma clearance is 15.9 (5.3) L/hour. Mean (SD) renal clearance is 10.8 (3.5) L/hour. The magnitude of this value, coupled with the significant decrease in the elimination of doripenem with concomitant probenecid administration, suggests that doripenem undergoes both glomerular filtration and active tubular secretion. In healthy adults given a single 500 mg dose of DORIBAX™, a mean of 70% and 15% of the dose was recovered in urine as unchanged drug and the ring-opened metabolite, respectively, within 48 hours. Following the administration of a

single 500 mg dose of radiolabeled doripenem to healthy adults, less than 1% of the total radioactivity was recovered in feces after one week.

- **Special Populations**

**Patients with Renal Impairment**

Following a single 500 mg dose of DORIBAX™, the mean AUC of doripenem in subjects with mild (CrCl 50-79 mL/min), moderate (CrCl 31-50 mL/min), and severe renal impairment (CrCl ≤30 mL/min) was 1.6-, 2.8-, and 5.1-times that of age-matched healthy subjects with normal renal function (CrCl ≥80 mL/min), respectively. Dosage adjustment is necessary in patients with moderate and severe renal impairment. [see *Dosage and Administration (2.2)*]

A single 500 mg dose of DORIBAX™ was administered to subjects with end stage renal disease (ESRD) either one hour prior to or one hour after hemodialysis (HD). The mean doripenem AUC following the post-HD infusion was 7.8-times that of healthy subjects with normal renal function. The mean total recovery of doripenem and doripenem-M1 in the dialysate following a 4-hour HD session was 231 mg and 28 mg, respectively, or a total of 259 mg (52% of the dose). There is insufficient information to make dose adjustment recommendations in patients on hemodialysis.

**Patients with Hepatic Impairment**

The pharmacokinetics of doripenem in patients with hepatic impairment have not been established. As doripenem does not appear to undergo hepatic metabolism, the pharmacokinetics of doripenem are not expected to be affected by hepatic impairment.

**Geriatric Patients**

The impact of age on the pharmacokinetics of doripenem was evaluated in healthy male (n=6) and female (n=6) subjects ≥ 66 years of age. Mean doripenem $AUC_{0-\infty}$ was 49% higher in elderly adults relative to non-elderly adults. This difference in exposure was mainly attributed to age-related changes in creatinine clearance. No dosage adjustment is recommended for elderly patients with normal (for their age) renal function.

**Gender**

The effect of gender on the pharmacokinetics of doripenem was evaluated in healthy male (n=12) and female (n=12) subjects. Doripenem $C_{max}$ and AUC were similar between males and females. No dose adjustment is recommended based on gender.

**Race**

The effect of race on doripenem pharmacokinetics was examined using a population pharmacokinetic analysis of data from phase 1 and 2 studies. Compared to Caucasians, mean doripenem clearance was 14% greater in Hispanic/Latino subjects whereas no difference in clearance was observed for African Americans. Doripenem clearance in Japanese studies is similar to what has been observed in Western populations. No dosage adjustment is recommended based on race.

- **Drug Interactions**

Probenecid interferes with the active tubular secretion of doripenem, resulting in increased plasma concentrations. Probenecid increased doripenem AUC by 75% and prolonged the plasma elimination half-life by 53%. [see also *Drug Interactions (7.2)*]

*In vitro* studies in human liver microsomes and hepatocytes indicate that doripenem does not inhibit the major cytochrome P450 isoenzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A11). Therefore, DORIBAX™ is not expected to inhibit the clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner.

DORIBAX™ is also not expected to have CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP3A4/5, or UGT1A1 enzyme-inducing properties based on *in vitro* studies in cultured human hepatocytes.

## 12.4 Microbiology

- **Mechanism of Action**

Doripenem belongs to the carbapenem class of antimicrobials. Doripenem exerts its bactericidal activity by inhibiting bacterial cell wall biosynthesis. Doripenem inactivates multiple essential penicillin-binding proteins (PBPs) resulting in inhibition of cell wall synthesis with subsequent cell death. In *E. coli* and *P. aeruginosa,* doripenem binds to PBP 2, which is involved in the maintenance of cell shape, as well as to PBPs 3 and 4.

- **Mechanism(s) of Resistance**

Bacterial resistance mechanisms that affect doripenem include drug inactivation by carbapenem-hydrolyzing enzymes, mutant or acquired PBPs, decreased outer membrane permeability and active efflux. Doripenem is stable to hydrolysis by most beta-lactamases, including penicillinases and cephalosporinases produced by Gram-positive and Gram-negative bacteria, with the exception of carbapenem hydrolyzing beta-lactamases. Although cross-resistance may occur, some isolates resistant to other carbapenems may be susceptible to doripenem.

- **Interaction with Other Antimicrobials**

*In vitro* synergy tests with doripenem show doripenem has little potential to antagonize or be antagonized by other antibiotics (e.g., levofloxacin, amikacin, trimethoprim-sulfamethoxazole, daptomycin, linezolid, and vancomycin).

Doripenem has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections. [see *Indications and Usage (1)*]

**Facultative Gram-negative microorganisms**

*Acinetobacter baumannii*
*Escherichia coli*
*Klebsiella pneumoniae*
*Proteus mirabilis*
*Pseudomonas aeruginosa*

**Facultative Gram-positive microorganisms**

*Streptococcus constellatus*
*Streptococcus intermedius*

**Anaerobic microorganisms**

*Bacteroides caccae*
*Bacteroides fragilis*
*Bacteroides thetaiotaomicron*
*Bacteroides uniformis*
*Bacteroides vulgatus*
*Peptostreptococcus micros*

At least 90 percent of the following microorganisms exhibit an *in vitro* minimal inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for doripenem of organisms of the same type shown in Table 6. The safety and efficacy of doripenem in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials.

**Facultative Gram-positive microorganisms**

*Staphylococcus aureus* (methicillin-susceptible isolates only)
*Streptococcus agalactiae*
*Streptococcus pyogenes*

**Facultative Gram-negative microorganisms**

*Citrobacter freundii*
*Enterobacter cloacae*
*Enterobacter aerogenes*
*Klebsiella oxytoca*
*Morganella morganii*
*Serratia marcescens*

- **Susceptibility Test Methods**

When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

**Dilution Techniques**

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method [1,3] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of doripenem powder. The MIC values should be interpreted according to the criteria provided in Table 6.

**Diffusion Techniques**

Quantitative methods that require measurement of zone diameters provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure [2,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10 µg of doripenem to test the susceptibility of microorganisms to doripenem. Results should be interpreted according to the criteria in Table 6.

**Anaerobic Techniques**

For anaerobic bacteria, the susceptibility to doripenem as MICs should be determined by standardized test methods [4]. The MIC values obtained should be interpreted according to the criteria in Table 6.

Table 6. Susceptibility Test Result Interpretive Criteria for Doripenem

| | Minimum Inhibitory Concentrations (μg/mL) | Disk Diffusion (zone diameters in mm) |
|---|---|---|
| Pathogen | Susceptible[a] | Susceptible |
| *Enterobacteriaceae* | ≤0.5 | ≥23 |
| *Pseudomonas aeruginosa* | ≤2 | ≥24 |
| *Acinetobacter baumannii* | ≤1 | ≥17 |
| *Streptococcus anginosus* group (*S. constellatus* and *S. intermedius)* | ≤0.12 | ≥24 |
| *Anaerobes* | ≤1 | n/a[b] |

[a] The current absence of resistant isolates precludes defining any results other than "Susceptible". Isolates yielding MIC or disk diffusion results suggestive of "Nonsusceptible" should be subjected to additional testing.
[b] n/a = not applicable

A report of *Susceptible* indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentrations usually achievable.

### Quality Control

Standardized susceptibility test procedures require the use of laboratory control microorganisms to monitor the performance of the supplies and reagents used in the assay, and the techniques of the individuals performing the test. Standard doripenem powder should provide the MIC values provided in Table 7. For the diffusion techniques using a 10 μg doripenem disk, the criteria noted in Table 7 should be achieved.

Table 7. Acceptable Quality Control Ranges for Susceptibility Testing

| QC Organism | Minimum Inhibitory Concentrations (μg/mL) | Disk Diffusion (zone diameters in mm) |
|---|---|---|
| *Escherichia coli* ATCC 25922 | 0.015-0.06 | 28-35 |
| *Pseudomonas aeruginosa* ATCC 27853 | 0.12-0.5 | 29-35 |
| *Streptococcus pneumoniae* ATCC 49619[a] | 0.03-0.12 | 30-38 |
| *Bacteroides fragilis* ATCC 25285 | 0.12-0.5 | n/a |
| *Bacteroides thetaiotaomicron* ATCC 29741 | 0.12-1 | n/a |

[a] This organism may be used for validation of susceptibility test results when testing organisms of the *Streptococcus anginosus* group

## 13 NON-CLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Because of the short duration of treatment and intermittent clinical use, long-term carcinogenicity studies have not been conducted with doripenem.

Doripenem did not show evidence of mutagenic activity in standard tests that included bacterial reverse mutation assay, chromosomal aberration assay with Chinese hamster lung fibroblast cells, and mouse bone marrow micronucleus assay.

Intravenous injection of doripenem had no adverse effects on general fertility of treated male and female rats or on postnatal development and reproductive performance of the offspring at doses as high as 1g/kg/day (based on AUC, greater than 1.5 times the exposure to humans at the dose of 500 mg q8h).

## 14 CLINICAL STUDIES

### 14.1 Complicated Intra-Abdominal Infections

A total of 946 adults with complicated intra-abdominal infections were randomized and received study medications in two identical multinational, multi-center, double-blind studies comparing DORIBAX™ (500 mg administered over 1 hour q8h) to meropenem (1 g administered over 3-5 minutes q8h). Both regimens allowed the option to switch to oral amoxicillin/clavulanate (875 mg/125 mg twice daily) after a minimum of 3 days of intravenous therapy for a total of 5-14 days of intravenous and oral treatment. Patients with complicated appendicitis, or other complicated intra-abdominal infections, including bowel perforation, cholecystitis, intra-abdominal or solid organ abscess and generalized peritonitis were enrolled.

DORIBAX™ was non-inferior to meropenem with regard to clinical cure rates in microbiologically evaluable (ME) patients, i.e., in patients with susceptible pathogens isolated at baseline and no major protocol deviations at test of cure (TOC) visit, 25-45 days after completing therapy. DORIBAX™ was also non-inferior to meropenem in microbiological modified intent-to-treat (mMITT) patients, i.e., patients with baseline pathogens isolated regardless of susceptibility. Clinical cure rates at TOC are displayed by patient populations in Table 8. Microbiological cure rates at TOC by pathogen in ME patients are presented in Table 9.

Table 8. Clinical Cure Rates in Two Phase 3 Studies of Adults with Complicated Intra-Abdominal Infections

| Analysis Populations | DORIBAX™ [a] n/N (%)[c] | Meropenem[b] n/N (%)[c] | Treatment Difference (2-sided 95% CI[f]) |
|---|---|---|---|
| **Study 1:** | | | |
| ME[d] | 130/157 (82.8) | 128/149 (85.9) | -3.1 (-11.3; 5.2) |
| mMITT[e] | 143/194 (73.7) | 149/191 (78.0) | -4.3 (-12.8; 4.3) |
| **Study 2:** | | | |
| ME[d] | 128/158 (81.0) | 119/145 (82.1) | -1.1 (-9.8; 7.8) |
| mMITT[e] | 143/199 (71.9) | 138/186 (74.2) | -2.3 (-11.2; 6.6) |

[a] 500 mg administered over 1 hour q8h
[b] 1 g administered over 3 - 5 minutes q8h
[c] n = number of patients in the designated population who were cured; N = number of patients in the designated population
[d] ME = microbiologically evaluable patients
[e] mMITT = microbiological modified intent-to-treat patients
[f] CI = confidence interval

**Table 9. Microbiological Cure Rates by Infecting Pathogen in Microbiologically Evaluable Adults with Complicated Intra-abdominal Infections**

| Pathogen | DORIBAX™ | | | Meropenem | | |
|---|---|---|---|---|---|---|
| | N[a] | n[b] | % | N[a] | n[b] | % |
| **Gram-positive, aerobic** | | | | | | |
| *Streptococcus constellatus* | 10 | 9 | 90.0 | 7 | 5 | 71.4 |
| *Streptococcus intermedius* | 36 | 30 | 83.3 | 29 | 21 | 72.4 |
| **Gram-positive, anaerobic** | | | | | | |
| *Peptostreptococcus micros* | 13 | 11 | 84.6 | 14 | 11 | 78.6 |
| **Gram-negative, aerobic** | | | | | | |
| *Enterobacteriaceae* | 315 | 271 | 86.0 | 274 | 234 | 85.4 |
| *Escherichia coli* | 216 | 189 | 87.5 | 199 | 168 | 84.4 |
| *Klebsiella pneumoniae* | 32 | 25 | 78.1 | 20 | 19 | 95.0 |
| Non-fermenters | 51 | 44 | 86.3 | 39 | 28 | 71.8 |
| *Pseudomonas aeruginosa* | 40 | 34 | 85.0 | 32 | 24 | 75.0 |
| **Gram-negative, anaerobic** | | | | | | |
| Bacteroides fragilis group | 173 | 152 | 87.9 | 181 | 152 | 84.0 |
| *Bacteroides caccae* | 25 | 23 | 92.0 | 19 | 18 | 94.7 |
| *Bacteroides fragilis* | 67 | 56 | 83.6 | 68 | 54 | 79.4 |
| *Bacteroides thetaiotaomicron* | 34 | 30 | 88.2 | 36 | 32 | 88.9 |
| *Bacteroides uniformis* | 22 | 19 | 86.4 | 18 | 15 | 83.3 |
| Non-fragilis Bacteroides | 14 | 13 | 92.9 | 13 | 9 | 69.2 |
| *Bacteroides vulgatus* | 11 | 11 | 100.0 | 8 | 6 | 75.0 |

[a] N = number of unique baseline isolates
[b] n = number of pathogens assessed as cured

## 14.2 Complicated Urinary Tract Infections, Including Pyelonephritis

A total of 1171 adults with complicated urinary tract infections, including pyelonephritis (49 percent of microbiologically evaluable patients) were randomized and received study medications in two multi-center, multinational studies. Complicated pyelonephritis, i.e., pyelonephritis associated with predisposing anatomical or functional abnormality, comprised

17% of patients with pyelonephritis. One study was double-blind and compared DORIBAX™ (500 mg administered over 1 hour q8h) to IV levofloxacin (250 mg q24h). The second study was a non-comparative study but of otherwise similar design. Both studies permitted the option of switching to oral levofloxacin (250 mg every q24h) after a minimum of 3 days of IV therapy for a total of 10 days of treatment. Patients with confirmed concurrent bacteremia were allowed to receive 500 mg of IV levofloxacin (either IV or oral as appropriate) for a total of 10 to 14 days of treatment.

DORIBAX™ was non-inferior to levofloxacin with regard to the microbiological eradication rates in microbiologically evaluable (ME) patients, i.e., patients with baseline uropathogens isolated, no major protocol deviations and urine cultures at test of cure (TOC) visit 5-11 days after completing therapy. DORIBAX™ was also non-inferior to levofloxacin in microbiological modified intent-to-treat (mMITT) patients, i.e., patients with pretreatment urine cultures. Overall microbiological eradication rates at TOC and the 95% CIs for the comparative study are displayed in Table 10. Microbiological eradication rates at TOC by pathogen in ME patients are presented in Table 11.

**Table 10. Microbiological Eradication Rates from the Phase 3 Comparative Study of Adults with Complicated Urinary Tract Infections, Including Pyelonephritis**

| Analysis populations | DORIBAX™ [a] n/N (%)[c] | Levofloxacin[b] n/N (%)[c] | Treatment Difference (2-sided 95% CI[f]) |
|---|---|---|---|
| ME [d] | 230/280 (82.1) | 221/265 (83.4) | -1.3 (-8.0, 5.5) |
| mMITT [e] | 259/327 (79.2) | 251/321 (78.2) | 1.0 (-5.6, 7.6) |

[a] 500 mg administered over 1 hour q8h
[b] 250 mg administered intravenously q24h
[c] n = number of patients in the designated population who were cured; N = number of patients in the designated population
[d] ME = microbiologically evaluable patients
[e] mMITT = microbiological modified intent-to-treat patients
[f] CI= confidence interval

Table 11. Microbiological Eradication Rates By Infecting Pathogen in Microbiologically Evaluable Adults with Complicated Urinary Tract Infections, Including Pyelonephritis

| Pathogen | DORIBAX™ [a] | | | Levofloxacin | | |
|---|---|---|---|---|---|---|
| | N[b] | n[c] | % | N[b] | n[c] | % |
| **Gram-negative, aerobic** | | | | | | |
| *Escherichia coli* | 357 | 313 | 87.7 | 211 | 184 | 87.2 |
| *Klebsiella pneumoniae* | 33 | 26 | 78.8 | 8 | 5 | 62.5 |
| *Proteus mirabilis* | 30 | 22 | 73.3 | 15 | 13 | 86.7 |
| Non-fermenters | 38 | 27 | 71.1 | 8 | 5 | 62.5 |
| *Acinetobacter baumannii* | 10 | 8 | 80.0 | 1 | 0 | 0.0 |
| *Pseudomonas aeruginosa* | 27 | 19 | 70.4 | 7 | 5 | 71.4 |

[a] data from comparative and non-comparative studies
[b] N = number of unique baseline isolates
[c] n = number of pathogens with a favorable outcome (eradication)

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3. CLSI. Performance Standards for Antimicrobial Susceptibility Testing; 17th Informational Supplement. CLSI document M100-S17. CLSI, Wayne, PA 19087, 2007.

4. CLSI. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard – 7th ed. CLSI document M11-A7. CLSI, Wayne, PA 19087, 2007.


## 16 HOW SUPPLIED/STORAGE AND HANDLING

- DORIBAX™ is supplied as single use type 1 clear glass vials containing 500 mg (on an anhydrous basis) of sterile doripenem powder. Vials are packaged individually (NDC: 0062-4010-01) in cartons containing 10 vials (NDC: 0062-4010-02).

- Storage of DORIBAX vials: DORIBAX™ should be stored at 25°C (77°F); excursions permitted to 15°-30°C (59° to 86°F) [refer to USP controlled room temperature].

## 17 PATIENT COUNSELING INFORMATION

- Patients should be advised that allergic reactions, including serious allergic reactions, could occur and that serious reactions require immediate treatment. They should report

any previous hypersensitivity reactions to DORIBAX™, other carbapenems, beta-lactams or other allergens.

- Patients should be counseled that anti-bacterial drugs including DORIBAX™ should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When DORIBAX™ is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by DORIBAX™ or other antibacterial drugs in the future.

- Keep out of the reach of children.

MINI-BAG Plus is a trademark of Baxter International Inc.

Manufactured by: Shionogi & Co. Ltd.
Osaka 541-0045, Japan

Distributed by: Ortho-McNeil Pharmaceutical, Inc.
Raritan, NJ 08869

**Exhibit 2**

**Copy of U.S. Patent No. 5,317,016 and Certificate of Correction**

US005317016A

# United States Patent [19]

Nishitani et al.

[11] Patent Number: 5,317,016

[45] Date of Patent: May 31, 1994

[54] PYRROLIDYLTHIOCARBAPENEM DERIVATIVE

[75] Inventors: Yasuhiro Nishitani; Tadashi Irie, both of Osaka, Japan

[73] Assignee: Shionogi Seiyaku Kabushiki Kaisha, Osaka, Japan

[21] Appl. No.: 929,961

[22] Filed: Aug. 14, 1992

[30] Foreign Application Priority Data

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Feb. 21, 1992 [JP] Japan ..... 4-35366

[51] Int. Cl.[5] ..... C07D 487/04; A61K 31/40

[52] U.S. Cl. ..... 514/210; 540/350; 540/310

[58] Field of Search ..... 540/350, 310; 514/210

[56] References Cited

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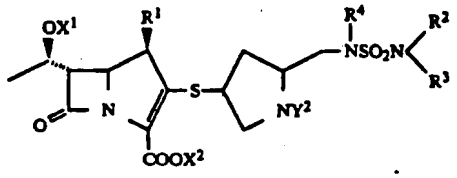
| 63-179876 | of 1988 | Japan . |

*Primary Examiner*—Nicholas S. Rizzo

*Attorney, Agent, or Firm*—Renner, Otto, Boisselle & Sklar

[57] ABSTRACT

A pyrrolidylthiocarbapenem derivative represented by Formula I is provided:



(I)

wherein $R^1$ is hydrogen or lower alkyl; $R^2$, $R^3$ and $R^4$ are hydrogen, lower alkyl which can be substituted or an amino protecting group independently, or $R^2$ and $R^3$ together with a nitrogen atom to which $R^2$ and $R^3$ are bonded form a saturated or unsaturated cyclic group, or $R^2$ and $R^4$, or $R^3$ and $R^4$ together with two nitrogen atoms and one sulfur atom in the sufamide group form a saturated or unsaturated cyclic group; each cyclic group can further include at least one atom selected from the group consisting of oxygen, sulfur and nitrogen, and each cyclic group can be substituted; $X^1$ is hydrogen or a hydroxy protecting group; $X^2$ is hydrogen, a carboxy protecting group, an ammonio group, an alkali metal or an alkaline-earth metal; and $Y^2$ is hydrogen or an amino protecting group.

16 Claims, No Drawings

# PYRROLIDYLTHIOCARBAPENEM DERIVATIVE

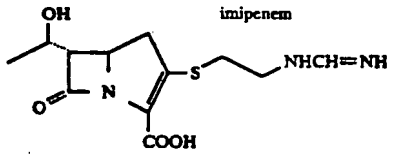
## BACKGROUND OF THE INVENTION

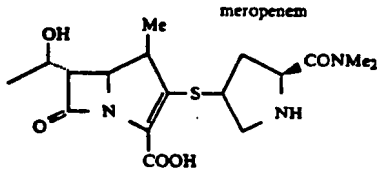
1. Field of the Invention

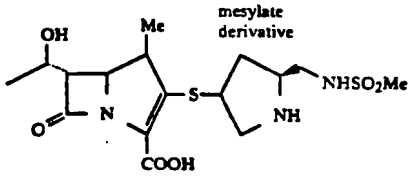
The present invention relates to a new pyrrolidylthiocarbapenem derivative having a wide range of antibacterial spectrum, an antibacterial agent comprising the carbapenem derivative, a new pyrrolidine derivative which is an intermediate for producing the carbapenem derivative, and a method for producing the pyrrolidylthiocarbapenem derivative and the pyrrolidine derivative.

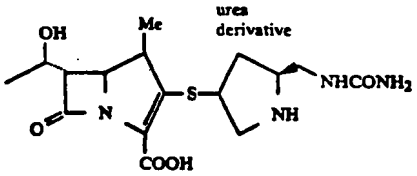
2. Description of the Prior Art

Various compounds are known as carbapenems, a kind of a β-lactam antibiotic. For example, imipenem, meropenem, the mesylate (mesylamino), and the urea derivatives of a carbapenem as shown below are known.



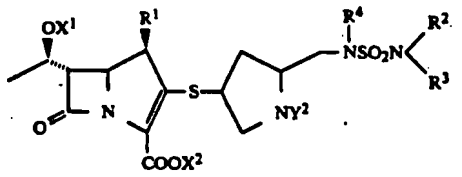




All of these compounds have a wide range of antibacterial spectrum, and are effective against both Gram-positive bacteria and Gram-negative bacteria. A carbapenem derivative having a wider range of antibacterial spectrum and a stronger antimicrobial activity has been desired.

## SUMMARY OF THE INVENTION

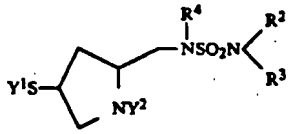
The pyrrolidylthiocarbapenem derivative of this invention is represented by Formula I:




(I)

wherein $R^1$ is hydrogen or lower alkyl; $R^2$, $R^3$ and $R^4$ are hydrogen, lower alkyl which can be substituted or an amino protecting group independently, or $R^2$ and $R^3$ together with a nitrogen atom to which $R^2$ and $R^3$ are bonded form a saturated or unsaturated cyclic group, or $R^2$ and $R^4$, or $R^3$ and $R^4$ together with two nitrogen atoms and one sulfur atom in the sufamide group form a saturated or unsaturated cyclic group; each cyclic group can further include at least one atom selected from the group consisting of oxygen, sulfur and nitrogen, and each cyclic group can be substituted; $X^1$ is hydrogen or a hydroxy protecting group; $X^2$ is hydrogen, a carboxy protecting group, an ammonio group, an alkali metal or an alkaline-earth metal; and $Y^2$ is hydrogen or an amino protecting group.

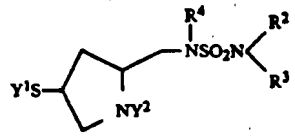
In another aspect of the present invention, the pyrrolidine derivative of the present invention is represented by Formula II:




(II)

wherein $R^2$, $R^3$ and $R^4$ are hydrogen, lower alkyl which can be substituted, or an amino protecting group independently, or $R^2$ and $R^3$ together with a nitrogen atom to which $R^2$ and $R^3$ are bonded form a saturated or unsaturated cyclic group, or $R^2$ and $R^4$, or $R^3$ and $R^4$ together with two nitrogen atoms and one sulfur atom in the sufamide group form a saturated or unsaturated cyclic group; each cyclic group can further include at least one atom selected from the group consisting of oxygen, sulfur and nitrogen, and each cyclic group can be substituted; $Y^1$ is hydrogen or a mercapto protecting group; and $Y^2$ is hydrogen or an amino protecting group.

Alternatively, the present invention provides a method for producing a pyrrolidine derivative represented by Formula II:



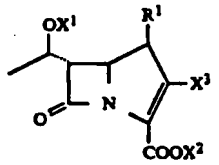

(II)

wherein $R^2$, $R^3$ and $R^4$ are hydrogen, lower alkyl which can be substituted, or an amino protecting group independently, or $R^2$ and $R^3$ together with a nitrogen atom to which $R^2$ and $R^3$ are bonded form a saturated or unsaturated cyclic group, or $R^2$ and $R^4$, or $R^3$ and $R^4$ together with two nitrogen atoms and one sulfur atom in the sufamide group form a saturated or unsaturated cyclic group; each cyclic group can further include at least one atom selected from the group consisting of

oxygen, sulfur and nitrogen, and each cyclic group can be substituted; $Y^1$ is hydrogen or a mercapto protecting group; and $Y^2$ is hydrogen or an amino protecting group; and

the method comprises the steps of: converting a hydroxy group at the 4-position of a 4-hydroxypyrrolidine-2-carboxylic acid derivative into a mercapto group; converting a carboxy group at the 2-position into a hydroxymethyl group; converting a hydroxy group in the hydroxymethyl group into an amino group or a sulfamoyl group; and converting the amino group into a sulfamoyl group.

Alternatively the present invention provides a method for producing a pyrrolidylthiocarbapenem derivative comprising the step of: allowing a carbapenem derivative to react with the pyrrolidine derivative of Formula II to obtain the pyrrolidylthiocarbapenem derivative of Formula I; the carbapenem derivative being represented by Formula III:




(III)

wherein $R^1$ is hydrogen or lower alkyl; $X^1$ is hydrogen or a hydroxy protecting group; $X^2$ is hydrogen, a carboxy protecting group, an ammonio group, an alkali metal or an alkaline-earth metal; and $X^3$ is a leaving group (e.g., reactive ester group of hydroxy, alkylsulfinyl arylsulfinyl, alkylsulfonyl, or arylsulfonyl).

Thus, the invention described herein makes possible the advantages of (1) providing a new carbapenem derivative having a strong antimicrobial activity and a wide range of antibacterial spectrum, and a method for producing the carbapenem derivative; (2) providing a new pyrrolidine derivative which is an intermediate for producing the carbapenem derivative, and a method for producing the pyrrolidine derivative; and (3) providing an antibacterial agent comprising the carbapenem derivative.

These and other advantages of the present invention will become apparent to those skilled in the art upon reading and understanding the following detailed description.

## DESCRIPTION OF THE PREFERRED EMBODIMENTS

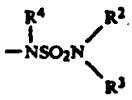
Followings are abbreviations used herein:

Ac: acetyl
Alz: allyloxycarbonyl
Boc: t-butoxycarbonyl
Et: ethyl
Ft: phthalyl
Me: methyl
Ms: methanesulfonyl
NPrc: protected amino
Ph: phenyl
PMB: p-methoxybenzyl
Pmz: p-methoxybenzyloxycarbonyl
PNB: p-nitrobenzyl
Pnz: p-nitrobenzyloxycarbonyl
Tr: trityl
Ts: p-toluenesulfonyl

A preferred scope of each group herein is as follows:

The number of carbon atoms of "lower alkyl" is 1 to 6. Examples of such an alkyl group include methyl, ethyl, n-propyl, iso-propyl, n-butyl, t-butyl, pentyl and hexyl. The number of carbon atoms of the lower alkyl is preferably 1 to 4. The most preferred lower alkyl is methyl or ethyl. Examples of a substituent of "a substituted lower alkyl" include hydroxy, alkoxy, amino, acylamino, lower alkylamino, carbamoyl, lower alkylcarbamoyl, lower alkylcarbamoyloxy and cyano. The number of carbon atoms of "aralkyl" is 7 to 15. Examples of "an amino protecting group" and "a hydroxy protecting group" include lower alkoxycarbonyl, lower alkenyloxycarbonyl, halogenoalkoxycarbonyl, aralkyloxycarbonyl, trialkylsilyl and diazo. An example of the lower alkoxycarbonyl includes t-butyloxycarbonyl; an example of the lower alkenyloxycarbonyl includes allyloxycarbonyl; examples of the halogenoalkoxycarbonyl include 2-iodoethyloxycarbonyl and 2,2,2-trichloroethyloxycarbonyl; examples of the aralkyloxycarbonyl include benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl and diphenylmethoxycarbonyl; examples of the trialkylsilyl include trimethylsilyl, triethylsilyl and t-butyldimethylsilyl.

In a definition of a group represented as follows:




[IIa]

a saturated or unsaturated cyclic group formed from $R^2$ and $R^3$ together with a nitrogen atom to which $R^2$ and $R^3$ are bonded can be, a saturated or unsaturated 3 to 8 membered residue further having one or more of nitrogen, sulfur and/or oxygen atoms, if necessary, and a 5 or 6 membered monocyclic residue including a hetero atom is preferable. The examples include pyrrolidin-1-yl, pyrrol-1-yl, imidazolidin-1-yl, imidazol-1-yl, pyrazolidin-1-yl, pyrazol-1-yl, piperidino, dihydro- or tetrahydropyridin-1-yl, piperazino, piperazin-1-yl which may have a substituent at the 4-position, morpholino and thiomorpholino. These groups may be substituted for one or more, preferably one or two, of the following groups: amino, protected amino, carbamoyl, lower alkyl, hydroxy, protected hydroxyl, lower alkoxy, oxo, lower alkylsulfonyl, hydroxy lower alkyl, carbamoyl lower alkyl, lower alkoxycarbonyl and cyano. Moreover, when the cyclic group is imidazolidin-1-yl, pyrazolidin-1-yl or piperazin-1-yl, the imino moiety thereof may be protected by a imino protecting group which is known in the art.

In the definition of the group IIa, a saturated or unsaturated cyclic group formed from $R^2$ and $R^4$, or $R^3$ and $R^4$ can be a saturated or unsaturated 5 to 7 membered residue having 2 to 3 nitrogen atoms and one sulfur atom and if necessary, having an another hetero atom such as an oxygen atom, and 5 to 6 membered monocyclic residue including a hetero atom is preferable. Such a residue may include, if necessary, a substituent such as lower alkyl, halogen, lower alkoxy, acyloxy, hydroxy, amino, lower alkylamino, acylamino and oxo, and/or an unsaturated bond. The examples include 1,1-dioxothiadiazinyl, 1,1-dioxodihydrothiadiazinyl, 1,1,3-trioxodihydrothiadiazinyl, 1,1-dioxothiadiazolizinyl, 1,1-dioxothiadiazolinyl, and 1,1,3-trioxothiadiazolinyl.

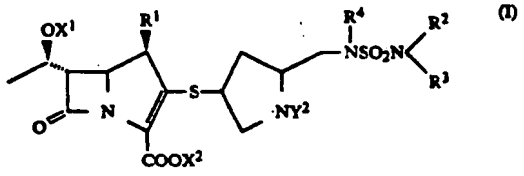
The "carboxy protecting group" is selected from those used in the art and serve the function of blocking the carboxyl group while reactions are carried out at other sites of the molecule. Such group generally contains less than about 19 carbon atoms and bind to a carboxyl group reversibly without affecting the other parts of the molecule. Typical examples include following groups: optionally substituted $C_1$–$C_8$ alkyl, for example, methyl, methoxymethyl, ethyl, ethoxymethyl, iodomethyl, propyl, isopropyl, butyl, isobutyl, ethoxyethyl, methylthioethyl, methanesulfonylethyl, trichloroethyl, t-butyl, and the like; optionally substituted $C_3$–$C_8$ alkenyl, for example, propenyl, allyl, isoprenyl, hexenyl, phenylpropenyl, dimethylhexenyl, and the like; optionally substituted $C_7$–$C_{19}$ aralkyl, for example, benzyl, methylbenzyl, dimethylbenzyl, methoxybenzyl, ethoxybenzyl, nitrobenzyl, aminobenzyl, diphenylmethyl, phenylethyl, trityl, di-t-butylhydroxybenzyl, phthalidyl, phenacyl, and the like; optionally substituted $C_6$–$C_{12}$ aryl, for example, phenyl, toluyl diisopropylphenyl, xylyl, trichlorphenyl, pentachlorophenyl, indanyl, and the like; optionally substituted $C_1$–$C_{12}$ amino which is, e.g., an ester with acetone oxime, acetophenone oxime, acetoaldoxime, N-hydroxysuccineimide, N-hydroxyphthalimide, or the like; optionally substituted $C_3$–$C_{12}$ hydrocarbonated silyl, for example, trimethylsilyl, dimethylmethoxysilyl, t-butyldimethylsilyl, and the like; optionally substituted $C_3$–$C_{12}$ hydrocarbonated stannyl, for example, trimethylstannyl, and the like. Another carboxy protecting group is a pharmaceutically active ester forming group. Examples of such a group include following groups: 1-(oxygen-substituted)-$C_2$ to $C_{15}$ alkyl groups, for example, a straight, branched, ringed, or partially ringed alkanoyloxyalkyl, such as acetoxymethyl, acetoxyethyl, propionyloxymethyl, pivaloyloxymethyl, pivaloyloxyethyl, cyclohexaneacetoxyethyl, cyclohexanecarbonyloxycyclohexylmethyl, and the like; $C_3$–$C_{15}$ alkoxycarbonyloxyalkyl such as ethoxycabonyloxyethyl, and the like; $C_2$–$C_8$ alkoxyalkyl, such as methoxymethyl, methoxyethyl, and the like; $C_4$–$C_8$ 2-oxacycloalkyls, such as tetraphdropyranyl, tetrahydrofuranyl, and the like; substituted $C_8$–$C_{12}$ aralkyls, for example, phenacyl, phthalidyl, and the like; $C_6$–$C_{12}$ aryl, for example, phenyl, xylyl, indanyl, and the like; $C_2$–$C_{12}$ alkenyl, for example, allyl, isoprenyl, 2-oxo-1,3-dioxolyl-4-ylmethyl, and the like. Among the above, a protecting group used to block the carboxyl group during reactions is usually removed at the final step of the reaction, and therefore its structure is not essential. Thus, as one of skilled in the art can easily appreciate, the carboxy protecting group can be selected from various equivalent groups including amides, acid anhydrides formed with carbonic acid or carboxylic acids, and the like as long as an aimed carboxyl group is protected properly.

An example of the lower alkyl includes t-butyl; examples of the lower alkenyl include allyl, isopentenyl and 2-butenyl; examples of the halogeno lower alkyl include 2-iodoethyl and 2,2,2-trichloroethyl; examples of the lower alkoxymethyl include methoxymethyl, ethoxymethyl and isobutoxymethyl; examples of the lower aliphatic acyloxymethyl include acetoxymethyl, propionyloxymethyl, butyryloxymethyl and pivaloyloxymethyl; examples of the 1-lower alkoxycarbonyloxyethyl include 1-methoxycarbonyloxyethyl and 1-ethoxycarbonyloxyethyl; and examples of the aralkyl include benzyl, p-methoxybenzyl, o-nitrobenzyl, p-nitrobenzyl and diphenylmethyl. Examples of "an alkali metal" include lithium, sodium and potassium, and sodium or potassium is preferred. Examples of "an alkaline-earth metal" include magnesium and calcium.

As "a mercapto protecting group", a conventional one, e.g., acyl and aryl substituted lower alkyl such as benzyl, phenethyl, trityl and benzhydryl are included. As "a reactive ester group of hydroxy", a conventional one, e.g., a residue such as substituted or unsubstituted arylsulfonyloxy, lower alkanesulfonyloxy, halogeno lower alkanesulfonyloxy, dialkylphosphonyloxy, diarylphosphoryloxy and halogeno are included. Examples of the arylsulfonyloxy include benzenesulfonnyloxy, p-toluenesulfonyloxy, p-nitrobenzenesulfonyloxy and p-bromobenzenesulfonyloxy; examples of the lower alkanesulfonyloxy include methanesulfonyloxy and ethanesulfonyloxy; an example of the halogeno lower alkanesulfonyloxy includes trifluoromethanesulfonyloxy; an example of the dialkylphospheoryloxy includes diethylphosphoryloxy; an example of the diarylphosphoryloxy includes diphenylphosphoryloxy; and examples of the halogeno include chloro, bromo and iodo.

An example of "an alkylsulfinyl group" includes methylsulfinyl, and an example of "an arylsulfinyl group" includes phenylsulfinyl.

The pyrrolidylthiocarbapenem derivative of the present invention is represented by the following Formula I:



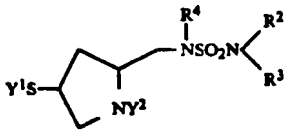

(I)

wherein $R^1$ is hydrogen or lower alkyl; $R^2$, $R^3$ and $R^4$ are hydrogen, lower alkyl which can be substituted or an amino protecting group independently, and preferably $R^4$ is hydrogen, or $R^2$ and $R^3$ together with a nitrogen atom to which $R^2$ and $R^3$ are bonded form a saturated or unsaturated cyclic group, or $R^2$ and $R^4$, or $R^3$ and $R^4$ together with two nitrogen atoms and one sulfur atom in the sulfamide group form a saturated or unsaturated cyclic group and each cyclic group can further include at least one atom selected from the group consisting of oxygen, sulfur and nitrogen, and each cyclic group can be substituted; $X^1$ is hydrogen or a hydroxy protecting group; $X^2$ is hydrogen, a carboxy protecting group, an ammonio group, an alkali metal or an alkaline-earth metal; and $Y^2$ is hydrogen or an amino protecting group.

When the above pyrrolidylthiocarbapenem derivative I has a free —OH, —COOH, amino group, imino group, or substituted amino group, the pyrrolidylthiocarbapenem also includes pharmaceutically acceptable salts thereof. The same is the case with an intermediate compound for synthesizing the pyrrolidylthiocarbapenem derivative such as the pyrrolidine derivative represented by Formula II. Examples of the pharmaceutically acceptable salts include a salt with a base, a salt with an acid, a salt with a basic or acidic amino acid and an intermolecular or intramolecular quarternary salt. Examples of the salt with a base include alkali metal salts such as sodium salt and potassium salt; alkaline-earth metal salts such as calcium salt and magne-

sium salt; ammonium salt; and organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt and dibenzylamine salt. Examples of the salt with an acid include inorganic acid addition salts such as hydrochloride, hydrobromide, sulfuric acid salt and phosphoric acid salt; and organic acid addition salts such as formic acid salt, acetic acid salt, trifluoroacetic acid salt, maleic acid salt, tartaric acid salt, methanesulfonic acid salt, benzenesulfonic acid salt and toluenesulfonic acid salt. Examples of the salt with an amino acid include a salt with arginine, aspartic acid or glutamic acid.

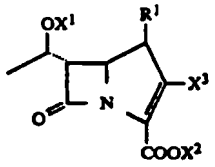
The pyrrolidylthiocarbapenem derivative (I) of the present invention can be produced in the steps of: by using, for example, 4-hydroxypyrrolidine-2-carboxylic acid or the derivative thereof as a starting material, obtaining a pyrrolidine derivative II represented by the following formula:



(II)

wherein $R^2$, $R^3$ and $R^4$ are hydrogen, lower alkyl which can be substituted, or an amino protecting group independently, and $R^4$ is preferably hydrogen, or $R^2$ and $R^3$ together with a nitrogen atom to which $R^2$ and $R^3$ are bonded form a saturated or unsaturated cyclic group, or $R^2$ and $R^4$, or $R^3$ and $R^4$ together with two nitrogen atoms and one sulfur atom in the sufamide group form a saturated or unsaturated cyclic group; each cyclic group can further include one atom selected from the group consisting of oxygen, sulfur and nitrogen, and each cyclic group can be substituted; $Y^1$ is hydrogen or a mercapto protecting group; and $Y^2$ is hydrogen or an amino protecting group; and

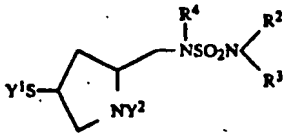
allowing the obtained pyrrolidine derivative II to react with a carbapenem derivative represented by the following Formula III:



(III)

wherein $R^1$ is hydrogen or lower alkyl; $X^1$ is hydrogen or a hydroxy protecting group; $X^2$ is hydrogen, a carboxy protecting group, an ammonio group, an alkali metal or an alkaline-earth metal; and $X^3$ is leaving group (e.g., a reactive ester of hydroxy, alkylsulfinyl, arylsulfinyl, alkylsulfonyl, or arylsulfonyl).

The present invention also includes a pyrrolidine derivative represented by the following Formula II:



(II)

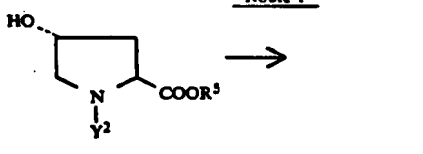
wherein $R^2$, $R^3$ and $R^4$ are hydrogen, substituent lower alkyl which can be substituted, or an amino protecting group independently, and $R^4$ is preferably hydrogen, or $R^2$ and $R^3$ together with a nitrogen atom to which $R^2$ and $R^3$ are bonded form a saturated or unsaturated cyclic group, or $R^2$ and $R^4$, or $R^3$ and $R^4$ together with two nitrogen atoms and one sulfur atom in the sufamide group form a saturated or unsaturated cyclic group; each cyclic group can further include at least one atom selected from the group consisting of oxygen, sulfur and nitrogen, and each cyclic group can be substituted; $Y^1$ is hydrogen or a mercapto protecting group; and $Y^2$ is hydrogen or an amino protecting group.

The pyrrolidine derivative II is prepared according to the steps of converting a hydroxy group at the 4-position of a 4-hydroxypyrrolidine-2-carboxylic acid derivative into a mercapto group; converting a carboxy group at the 2-position into a hydroxymethyl group; directly sulfamidating a hydroxy group in the hydroxymethyl group or sulfamoylating it after converting it into an amino group; and removing the protecting group $Y^1$ if necessary. The order of these steps can be properly changed.

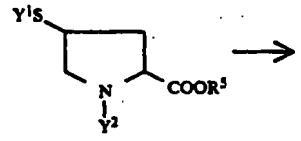
Synthesis of pyrrolidine derivative II

Pyrrolidine derivative II is synthesized, for example, in the following process, but is not limited to.

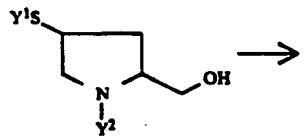
Route 1



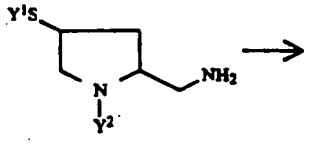
(IV)



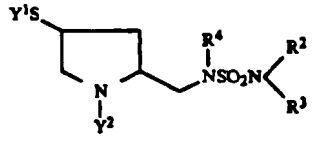
(V)



(VI)



(VIII)



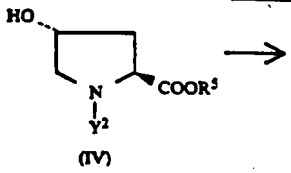
(II)

In the above scheme, $R^2$, $R^3$ and $R^4$ are the same as defined for Formula I, and $R^5$ is a group for forming an ester together with a carboxy group such as lower alkyl. $Y^1$ and $Y^2$ are the same as defined for Formulas I and II, but denote a mercapto protecting group and an amino protecting group, respectively, at the intermediate of the reaction route.

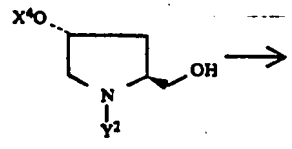
In this process, for example, 4-hydroxypyrrolidine-2-carboxylic acid derivative IV is first provided. A mesyl group or the like is introduced to the hydroxy group at the 4-position of compound IV, and then a protected mercapto group such as a tritylthio group is introduced to the 4-position. In this way, a compound V is obtained. Then, a compound VI is obtained by reducing a carboxylate group at the 2-position. An azide group is introduced to the compound VI, and the azide group is converted to an amino group, or phthalimide is reacted with the compound VI, and the formed phthalyl group is removed from the compound VI, thereby introducing an amino group at a position of the hydroxy group of the compound VI. Thus, a compound VII is obtained. A sulfamoyl group is then introduced to the compound VII to obtain a compound II.

Furthermore, the process of Route 1 can be variously modified. For example, after introducing a protected mercapto group to the 4-position of the compound IV, a carboxylate group is reduced and then a sulfamide group is introduced to obtain the compound II. Alternatively, after reducing the compound IV, a protected mercapto group and a sulfamide group are successively introduced to obtain the compound II.

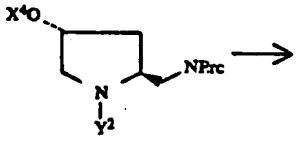
Route 2



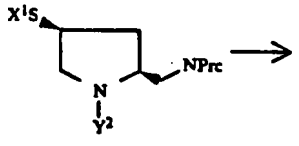
(IV)



(VIII)



(IX)



(X)

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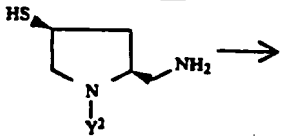
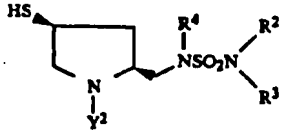
Route 2



(XI)



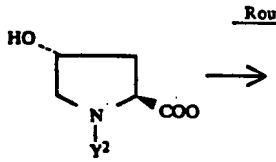
(II-1)

In the above scheme, $R^2$, $R^3$ and $R^4$ are the same as defined in Formula I, and $R^5$ is a group for forming ester together with a carboxy group such as lower alkyl. $Y^1$ and $Y^2$ are the same as defined in Formulas I and II, but denote a mercapto protecting group and an amino protecting group, respectively, at the intermediate of the reaction route. $X^4$ is a hydroxy protecting group.

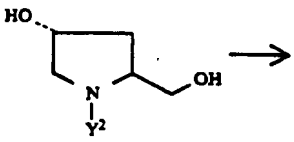
In this process, for example, a mesyl group or the like (represented by $X^4$) is first introduced to the 4-position of the 4-hydroxypyrrolidine-2-carboxylic acid derivative IV, then a carboxylate group is reduced to a hydroxymethyl group as is in Route 1 to obtain a compound VIII. Then, a protected amino group such as a phthalimide group is introduced to a position of a hydroxy group in the hydroxymethyl group. Thus a compound IX is obtained. In introducing the protected amino group, it is effective to introduce a leaving group to the hydroxy group of the compound VIII to increase the reactivity. Next, a mercapto group protected by thioacetate and the like (represented by $Y^1S$) is introduced to the 4-position (see a compound X), and removing the protection to obtain a compound XI. By introducing a sulfamoyl group to the compound XI, a compound II-1 (a compound II wherein the -SY' at the 2-position of the pyrrolidine ring is SH) is obtained.

Furthermore, the process of Route 2 can be variously modified. For example, by introducing a protected mercapto group to the 4-position of the compound VIII, further introducing a sulfamoyl group and removing the protection, the compound II-1 is obtained.

Route 3



(IV-1)



(XII)

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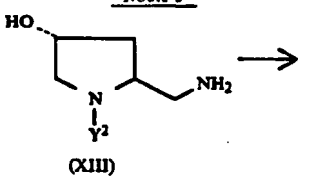
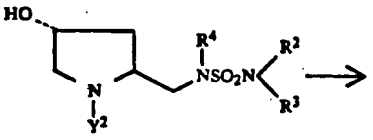
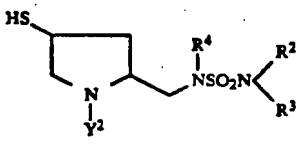
Route 3



(XIII)



(XIV)



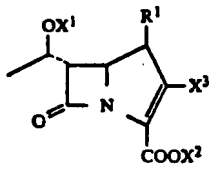
(II-1)

In the above scheme, $R^2$, $R^3$ and $R^4$ are the same as defined in Formula I. $Y^2$ is the same as defined in Formula I but denotes a protecting amino group at the intermediate of the reaction route.

In this method, chloroformate or the like is first allowed to react with 4-hydroxypyrrolidine-2-carboxylic acid IV-1 having protected nitrogen in the pyrrolidine ring. A carboxy group at the 2-position is then converted into a hydroxymethyl group by reduction. Next, after converting a hydroxy group in the hydroxymethyl group into a reactive ester and introducing a protected amino group, a compound XIII is obtained by removing the protection. A sulfamoyl group is introduced to the compound XIII resulting in a compound XIV, then, a protected mercapto group is introduced to a position of the hydroxy group at the 4-position. A compound II-1 is obtained by removing the protection of the mercapto group.

Synthesis of pyrrolidylthiocarbapenem derivative

The protection of the 4-position of the pyrrolidine derivative is removed to obtain an SH compound, if necessary, then, the pyrrolidine derivative is allowed to react with a carbapenem derivative represented by the following Formula III to give a pyrrolidylthiocarbapenem derivative I of the present invention:



(III)

wherein $R^1$ is hydrogen or lower alkyl; $X^1$ is hydrogen or a hydroxy protecting group; $X^2$ is hydrogen, a carboxy protecting group, an ammonio group, an alkali metal or an alkaline-earth metal; $X^3$ is a leaving group (e.g., reactive ester group of hydroxy, alkylsulfinyl, arylsulfinyl, alkylsulfonyl, or arylsufonyl).

The protection is removed from the compound I if necessary to give a compound having free carboxy, hydroxy and/or amino.

An antibacterial agent comprising the pyrrolidylthiocarbapenem derivative

A pharmaceutical composition comprising the pyrrolidylthiocarbapenem derivative (including pharmaceutically acceptable salts thereof) of the present invention is administered as an antibacterial agent. An administration method is in oral administration or parenteral administration; as injection (a formulation in an ampoule or vial, a liquid, a suspension or the like for an intravenous injection, an intramuscular injection, a drip infusion, or subcutaneous injection), an external or local administration agent (an ear drop, a nasal drop, an ophthalmic solution, an ointment, an emulsion, a spray, a suppository and the like), and an oral preparation. Preferably, the composition is administered by injection, through skin or mucosa. The pharmaceutical composition includes at least 0.01% by weight of the pyrrolidylthiocarbapenem derivative and further includes an appropriate excipient, auxiliary agent, stabilizer, wetting agent, emulsifier, and other additives depending upon the administration method. These additives must be pharmaceutically and pharmacologically acceptable materials which do not inhibit the effect of the pyrrolidylthiocarbapenem derivative and which show no adverse effects on patients. For example, lactose, stearic acid, magnesium stearate, clay, sucrose, cornstarch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter, ethylene glycol, tartaric acid, citric acid and fumaric acid can be contained in the oral preparation. For parenteral administration, a solvent (e.g., alcohol, a buffer, methyl oleate, water or the like), a buffer solution, a dispersing agent, a dissolving auxiliary agent, a stabilizer (e.g., methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, sorbic acid or the like), an absorbefacient (mono- or dioctanoate of glycerin), an antioxidant, a perfume, an analgetic, a dispersing agent, an adverse effect inhibitor, an action potentiator (an agent for regulating absorption and elimination, an inhibitor for enzyme decomposition, a $\beta$-lactamase inhibitor, and other kinds of antimicrobial agents) and the like can be contained in the formulation.

A dose of the pyrrolidylthiocarbapanem derivative of the present invention depends upon the age of a patient, the type and the state of the disease and the kind of compounds to be used. Generally, daily dose ranges from 1 mg/patient to about 4000 mg/patient, but more can be administered if necessary. For example, a dose of 1 mg (the external application) is administered 4 times a day, and a dose of 1000 mg (intravenous injection) is administered 2 to 4 times a day to treat an infection.

Characteristics of the pyrrolidylthiocarbapenem derivative

The characteristics of the pyrrolidylthiocarbapenem derivative of the present invention as an antibacterial agent will now be described as compared with same known compounds.

(1) Antimicrobial activity:

A minimum growth inhibitory concentration and an effect for preventing bacterial infection of the pyrrolidylthiocarbapenem derivative of the present invention are compared with those of meropenem (Japanese Laid Open Patent Publication No. 60-233076) and imipenem (Japanese Laid Open Patent Publication No.

55-9090), respectively to find that the derivative of the present invention is superior to meropenem against Gram positive bacteria and superior to imipenem against Gram negative bacteria. The derivative of the present invention has an antibacterial potency against *Pseudomonas aeruginosa*, a kind of a Gram negative bacteria, equal to or twice as that of imipenem, meropenem and the mesylamino derivative of a carbapenem (Japanese Laid Open Patent Publication No. 63-179876). When compared with the urea derivative of a carbapenem (Japanese Laid Open Patent Publication No. 62-155279), the derivative has equal to or twice the antibacterial potency against Gram positive bacteria, twice the potency against the Gram negative bacteria and twice to eight times the potency against *Pseudomonas aeruginosa*.

(2) Rabbit nephrotoxicity test:

An administration of the derivative of the present invention of 250 mg per 1 kg of the body weight of a rabbit reveals no toxicity. The same result is obtained by an administration of meropenem. When 150 mg/kg of imipenem is administered, medium renal toxicity is revealed. Sugar and protein are found in urine and a white microgranular change in the kidney is found.

(3) Rate of decomposition by mouse renal dehydropeptidase 1:

The enzymatic decomposition rate of the pyrrolidylthiocarbapenem derivative of the present invention by the action of renal dehydropeptidase I is 76% of that of imipenem, 40% of that of meropenem to show higher stability.

(4) Solubility in water:

The solubility in water of the derivative of the present invention is 10% or more in a form of free acid, enabling an intravenous injection. In contrast, the solubility of imipenem and meropenem is about 2% and they cannot be administered except for a drip infusion.

(5) Pharmacokinetics in vivo:

When the derivative of the present invention is intraveneously injected to a cynomolgus (10 mg/kg), the half-life is 1.1 hours, a recovery from urine is 62.2%, and an integrated value of a concentration in blood is 24.9 μg·hr/ml. The half-life is 1.44 times, the recovery from urine is 1.36 times and the integrated value of a concentration in blood (Area under the curve: AUC) is 1.44 times as much as those of meropenem. The half-life is 1.87 times, the recovery from urine is 1.93 times, and AUC is 1.87 times as much as those of imipenem.

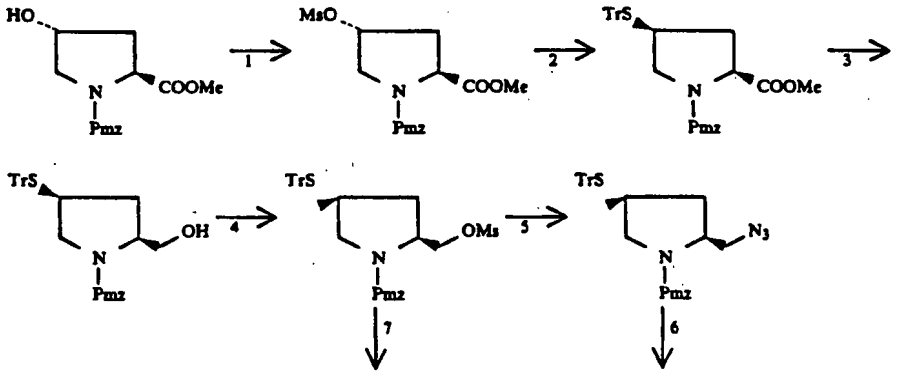
When the derivative is intravenously injected into a mouse (20 mg/kg), the recovery from urine is 36.3%, and the integrated value of a concentration in blood is 12.1 μg·hr/ml. The recovery from urine is 2.18 times and AUC is 2.32 times as much as those of meropenem. The recovery from urine is 1.15 times and AUC is 1.37 times as much as those of imipenem. The recovery from urine is 1.48 times as much as that of mesylate derivative of meropenem.

In this way, the present invention provides a new pyrrolidylthiocarbapenem derivative having a wide range of antibacterial spectrum and a strong antimicrobial activity against both Gram positive bacteria and Gram negative bacteria, an antibacterial agent (composition comprising the carbapenem derivative, and a method for preparing the carbapenem derivative. Furthermore, a new pyrrolidin derivative as an intermediate for preparing the carbapenem derivative and a method for preparing the same are provided.

A minimum bacterial growth inhibitory concentration and an effect for preventing bacterial infection of the pyrrolidylthiocarbapenem derivative of the present invention are compared with those of meropenem and imipenem, respectively to find that the derivative of the present invention is superior to meropenem against Gram positive bacteria and superior to imipenem against Gram negative bacteria. The derivative of the present invention has an antibacterial potency against *Pseudomonas aeruginosa*, a kind of a Gram negative bacterium, equal to or twice of that of imipenem, meropenem and the mesylamino derivative of a carbapenem. When compared with the urea derivative of a carbapenem, the derivative has an equal or twice the antibacterial potency against Gram positive bacteria, twice the potency against the Gram negative bacteria and twice to eight times the potency against *Pseudomonas aeruginosa*. The pyrrolidylthiocarbapenem derivative is less toxic to an organism that the conventional carbapenem derivatives. Since the derivative decomposes slowly in a body, the antimicrobial effect thereof lasts for a longer period of time. Moreover, since the derivative has a higher solubility in water than the conventional carbapenem derivatives, it can be applicable for injection.

Following Examples are given to show the present invention, but not to limit the scope thereof.

## PREPARATIVE EXAMPLE 1 OF A PYRROLIDINE DERIVATIVE



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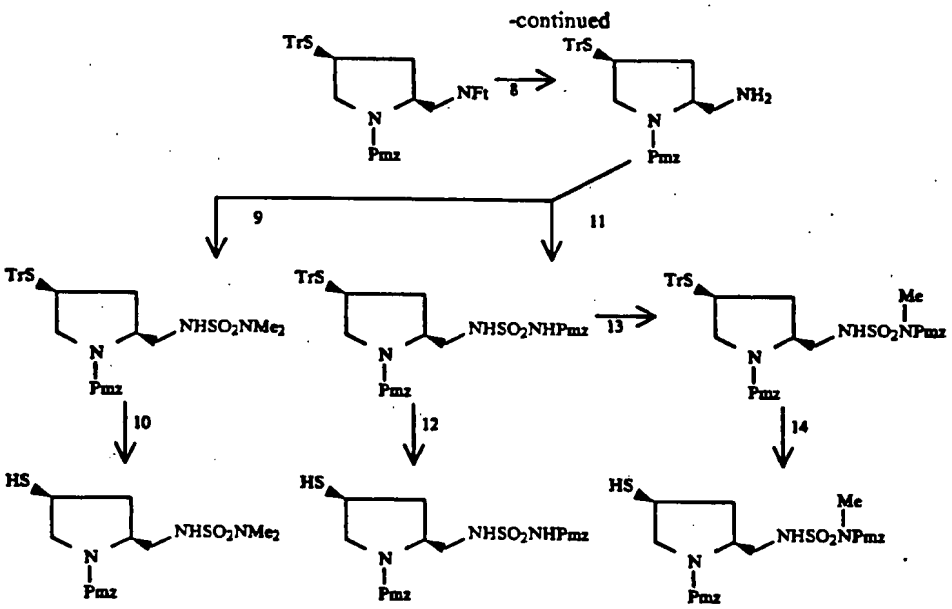



Step 1. Preparation of an O-mesyl compound

To a solution of (2S,4R)-1-p-methoxybenzyloxycarbonyl-4-hydroxypyrrolidine-2-carboxylic acid methyl ester (227.2 g: 0.735 mole) in dichloromethane (1.3 liter) stirring at −30° C., triethylamine (112.5 ml: 1.1 eq.) and methanesulfonyl chloride (56.8 ml: 1 eq.) are added. The mixture is stirred at the same temperature for 15 minutes. The reaction mixture is successively washed with dilute hydrochloric acid and water, dried over magnesium sulfate, and concentrated in vacuo to give (2s,4R)-1-p-methoxybenzyloxy-carbonyl-4-methanesulfonyloxypyrrolidine-2-carboxylic acid methyl ester (280.1 g). Yield: 98%. NMR δ($CDCl_3$) ppm: 3.02, 3.04(2×s, 3H), 3.56, 3.78(2×s, 3H), 3.81(s, 3H), 4.98, 5.08(ABq, J=12 Hz, 1H), 5.04, 5.12(ABq, J=12 Hz, 1H). IR ν ($CHCl_3$) $cm^{-1}$: 1755, 1709, 1620.

Step 2. Preparation of a tritylthio compound

To a solution of triphenylmethylmercaptan (107.02 g: 1.5 eq.) in dimethylformamide (350 ml), an oil suspension containing 60% sodium hydride (13.42 g: 1.3 eq.) is added with stirring at 0° C. The mixture is stirred at room temperature for 1 hour. The reaction mixture is mixed with a solution of (2S,4R)-1-p-methoxybenzyloxycarbonyl-4-methanesulfonyloxypyrrolidine-2-carboxylic acid methyl ester (100 g: 0.258 mole) in dimethylformamide(70 ml) with stirring at 0° C. The mixture is stirred at 60° C. for 30 minutes. The reaction mixture is poured into cold dilute hydrochloric acid, and extracted with ethyl acetate. The extract is successively washed with water and brine, dried, and concentrated in vacuo. The residue is purified by silica gel column chromatography (toluene:ethyl acetate=5:1) to give (2S,4S)-1-p-methoxybenzyloxycarbonyl-4-tritylthiopyrrolidine-2-carboxylic acid methyl ester (127.1 g). Yield: 87%. NMR δ($CDCl_3$) ppm: 3.50, 3.71(2×s, 3H), 3.78, 3.84(2×s, 3H), 4.87, 5.13(ABq, J=12 Hz, 1H), 4.89, 5.13(ABq, J=12 Hz, 1H). IR ν ($CHCl_3$) $cm^{-1}$: 1750, 1700, 1618.

Step 3. Preparation of a methylol compound

To a solution of (2S,4S)-1-p-methoxybenzyloxycarbonyl-4-tritylthiopyrrolidine-2-carboxylic acid methyl ester (127.1 g: 0.224 mole) in tetrahydrofuran (1 liter), lithium borohydride (4.88 g: 1 eq.) is added with stirring at room temperature. The mixture is stirred at 60° C. for 30 minutes. The reaction mixture is allowed to cool to room temperature and water (100 ml) is added in small portions with stirring. The formed precipitate is removed by filtration and the filtrate is concentrated in vacuo. The residue is dissolved in dichloromethane, dried over magnesium sulfate, and concentrated under reduced pressure. The residue is washed with ether to give (2S,4S)-1-p-methoxybenzyloxycarbonyl-4-tritylthiopyrrolidine-2-methanol as white crystals (82.3 g). Yield: 68%. NMR δ($CDCl_3$) ppm: 3.84(s, 3H), 4.93, 4.99(ABq, J=12 Hz, 2H). IR ν ($CHCl_3$) $cm^{-1}$: 3400, 1668, 1610.

Step 4. Preparation of a mesyl compound

A solution of (2S,4S)-1-p-methoxybenzyloxycarbonyl-4-tritylthiopyrrolidine-2-methanol (22.33 g: 41.37 mmole) is diluted with dichloromethane (300 ml) and the mixture is cooled to −30° C. To this mixture, triethylamine (6.92 ml: 1.2 eq.) and methanesulfonyl chloride (3.52 ml: 1.1 eq.) are added, and the mixture is stirred for 20 minutes. The reaction mixture is successively washed with dilute hydrochloric acid and water, dried over magnesium sulfate, and filtered. The filtrate is concentrated in vacuo to give crude (2S,4S)-1-p-methoxybenzyloxycarbonyl-4-tritylthiopyrrolidine-2-methanol methanesulfonate (27.81 g: 45.02 mmole). Yield: 100%. NMR δ($CDCl_3$) ppm: 2.89(s, 3H), 3.81, 3.83(2×s, 3H), 4.85 to 5.07(m, 2H). IR ν ($CHCl_3$) $cm^{-1}$: 1725, 1690, 1610.

Step 5. Preparation of an azide compound

To a solution of (2S,4S)-1-p-methoxybenzyloxycarbonyl-4-tritylthiopyrrolidine-2-methanol methanesulfonate (27.81 g) in dimethylformamide (120 ml), a solution (12 ml) of sodium azide (3.50 g: 53.8 mmole) in

water is added. The mixture is stirred at 80° C. for 8 hours. The reaction mixture is poured into ice water and extracted with ethyl acetate. The extract is successively washed with water and brine and concentrated. The residue is purified by silica gel column chromatography to give (2S,4S)-1-p-methoxybenzyloxycarbonyl-2-azidomethyl-4-tritylthiopyrrolidine (17.27 g: 30.64 mmole). Total yield of Steps 4 and 5: 74%. NMR $\delta(CDCl_3)$ ppm: 3.84(s, 3H), 4.82 to 5.15(m, 2H). IR $\nu$ ($CHCl_3$) $cm^{-1}$: 2105, 1685.

Step 6. Preparation of an amino compound

A solution of (2S,4S)-1-p-methoxybenzyloxycarbonyl-2-azidomethyl-4-tritylthiopyrrolidine (17.27 g: 30.64 mmole) in a mixture of ethyl acetate (150 ml), methanol (200 ml), and acetic acid (2.63 ml: 46 mmole) is subjected to conventional hydrogenation over 5% palladium on carbon (5 g). After the reaction, the catalyst is filtered off and the filtrate is concentrated in vacuo to give (2S,4S)-1-p-methoxybenzyloxycarbonyl-2-aminomethyl-4-tritylthiopyrrolidine acetate (17.33 g) as a residue. The residue is dissolved in dichloromethane, washed with aqueous sodium hydrogen carbonate, and concentrated to give (2S,4S)-2-aminomethyl-1-p-methoxybenzyloxycarbonyl-4-tritylthiopyrrolidine (16.82 g).

Step 7. Preparation of a phthalimido compound

Crude (2S,4S)-1-p-methoxybenzyloxycarbonyl-4-tritylthiopyrrolidine-2-methanol methanesulfonate (115.4 g) produced from (2S,4S)-1-p-methoxybenzyloxycarbonyl-4-tritylthiopyrrolidine-2-methanol (96.24 g: 178 mmole) in the same manner as in the above-mentioned Step 4 is dissolved in dimethylformamide (1 liter). After adding potassium phthalimide (65.94 g: 2 eq.), the mixture is stirred at 100° C. for 1 hour. The reaction mixture is poured into ice water and extracted with ethyl acetate. The extract is successively washed with water and brine, and concentrated. The residue is purified by silica gel column chromatography (toluene:ethyl acetate) to give (2S,4S)-1-p-methoxybenzyloxycarbonyl-2-phthalimidomethyl-4-tritylthiopyrrolidine (99.4 g). Yield: 83.5. NMR $\delta(CDCl_3)$ ppm: 3.78, 3.84(2×s, 3H), 4.65 to 5.00(m, 2H). IR $\nu$ ($CHCl_3$) $cm^{-1}$: 1770, 1712, 1693, 1611.

Step 8. Removal of a phthalyl group

To a solution of (2S,4S)-1-p-methoxybenzyloxycarbonyl-2-phthalimidomethyl-4-tritylthiopyrrolidine (752 mg: 1.124 mmole) in a mixture of dichloromethane (3 ml) and methanol (12 ml), hydrazine hydrate (109 μl: 2 eq.) is added. The mixture is heated for 5 hours. The reaction mixture is concentrated in vacuo. The residue is dissolved in dichloromethane (5 ml) and the solid is filtered off. The filtrate is washed with water and concentrated in vacuo. The residue is recrystallized from a mixture of dichloromethane and methanol to give (2S,4S)-1-p-methoxybenzyloxycarbonyl-2-aminomethyl-4-tritylthiopyrrolidine (471 mg). Yield: 78%. mp. 165° to 167° C. NMR $\delta(CDCl_3:CD_3OD=2:1)$ ppm: 3.46(s, 3H), 4.96, 4.89(ABq, J=12 Hz, 2H). IR $\nu$ ($CHCl_3$) $cm^{-1}$: 1683, 1610.

Step 9. Preparation of a dimethylsulfamoyl compound

A solution of (2S,4S)-1-p-methoxybenzyloxycarbonyl-2-aminomethyl-4-tritylthiopyrrolidine (12.44 g: 23.13 mmole) in dichloromethane(70 ml) is cooled to −78° C. After adding triethylamine (4.21 ml: 1.3 eq.) and dimethylaminosulfonyl chloride (2.73 ml: 1.1 eq.), the mixture is warmed to room temperature over about 1 hour. The reaction mixture is successively washed with dilute hydrochloric acid and brine, and concentrated to give crude (2S,4S)-1-p-methoxybenzyloxycarbonyl-2-N,N-dimethylsulfamoylaminomethyl-4-tritylthiopyrrolidine (15.02 g). Yield: 100%.

Step 10. Preparation of a mercapto compound by deprotection

To a solution of (2S,4S)-1-p-methoxybenzyloxycarbonyl-2-N,N-dimethylsulfamoylaminomethyl-4-tritylthipyrrolidine (3.55 g: 5.5 mmole) in a mixture of dichloromethane (70 ml) and methanol (35 ml), a solution of pyridine (0.66 ml: 1.5 eq.) and silver nitrate (1.40 g: 1.5 eq.) in water (3.5 ml) is added under ice cooling. The mixture is stirred for 10 minutes. The reaction mixture is poured into water and extracted with dichloromethane. The extract is dried over magnesium sulfate, bubbled with hydrogen sulfide, and filtered to remove solid. The filtrate is concentrated in vacuo and the residue is purified by silica gel column chromatography (toluene:ethyl acetate) to give (2S,4S)-1-p-methoxybenzyloxycarbonyl-2-N,N-dimethylsulfamoylaminomethyl-4-mercaptopyrrolidine (1.93 g). Yield: 87.0%. NMR $\delta(CDCl_3)$ ppm: 2.77(s, 6H), 3.81(s, 3H), 5.00 to 5.12(m, 2H). IR $\nu$ ($CHCl_3$) $cm^{-1}$: 3380, 1690, 1610.

Step 11. Preparation of a sulfamoyl compound

To a solution of chlorosulfonyl isocyanate (3.95 ml: 45.4 mmole) in dichloromethane (70 ml), p-methoxybenzyl alcohol (5.66 ml: 45.4 mmole) is added at −50° C. The mixture is stirred at −50° C. for 15 minutes. The resulting solution of p-methoxybenzyloxycarbonylsulfamoyl chloride is added to a solution of (2S,4S)-1-p-methoxybenzyloxycarbonyl-2-aminomethyl-4-tritylthiopyrrolidine (obtained in the above Steps 6 or 8) (12.21 g: 22.7 mmole) and triethylamine (6.38 ml: 45.6 mmole) in dichloromethane (300 ml) at −78° C., and the mixture is stirred for 10 minutes, successively washed with dilute hydrochloric acid and brine, and concentrated in vacuo. The residue is purified by silica gel column chromatography to give (2S,4S)-1-p-methoxybenzyloxycarbonyl-2-p-methoxybenzyloxycarbonylsulfamoylaminomethyl-4-tritylthiopyrrolidine (16.31 g). Yield: 91.6%. NMR $\delta(CDCl_3)$ ppm: 3.78(s, 3H), 3.81, 3.83(2×s, 3H), 4.98, 4.89(ABq, J=12 Hz, 2H), 5.09, 5.03(ABq, J=12 Hz, 2H). IR $\nu$ ($CHCl_3$) $cm^{-1}$: 3390, 1740, 1685.

Step 12. Preparation of a mercapto compound by deprotection

To a solution of (2S,4S)-1-p-methoxybenzyloxycarbonyl-2-p-methoxybenzyloxycarbonylsulfamoylaminomethyl-4-tritylthiopyrrolidine (2.35 g: 3.13 mmole) in a mixture of dichloromethane (60 ml) and methanol (30 ml), a solution of pyridine (0.38 ml: 4.75 mmole: 1.5 eq.) and silver nitrate (0.80 g: 1.5 eq.) in water (2 ml) is added under ice cooling. The mixture is stirred for 10 minutes. The reaction mixture is poured into water and extracted with dichloromethane. The extract is dried over magnesium sulfate and filtered. Hydrogen sulfide is passed through the filtrate and the resulting precipitate is filtered off. The filtrate is concentrated in vacuo and the residue is purified by silica gel column chromatography to give (2S,4S)-1-p-methoxybenzyloxycarbonyl-2-p-methoxybenzyloxycarbonylsulfamoylaminomethyl-4-mercaptopyrroli-

dine (1.56 g). Yield: 92.4%. NMR δ($CDCl_3$) ppm: 2.42 to 2.58(m, 1H), 3.80(s, 6H), 5.08, 5.02(ABq, J=12 Hz, 2H), 5.12, 5.07(ABq, J=16 Hz, 2H). IR ν ($CHCl_3$)$cm^{-1}$: 3380, 1740, 1685, 1610.

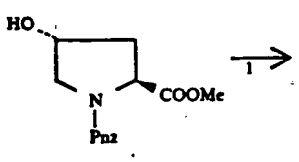
Step 13. Preparation of an N-methyl compound

To a solution of (2S,4S)-1-p-methoxybenzyloxycarbonyl-4-tritylthio-2-(p-methoxybenzyloxycarbonylaminosulfonylaminomethyl)pyrrolidine (2.06 g: 2.63 mmole) in dimethylformamide (15 ml), a solution of 1M-lithium bis(trimethylsilyl)amide in tetrahydrofuran (2.76 ml: 1.05 eq.) is added with stirring under ice cooling. After stirring for 1 hour, iodomethane (491 μl: 3 eq.) is added. The mixture is stirred at the same temperature for 3 hours. The reaction mixture is poured into a mixture of ethyl acetate and aqueous sodium sulfite and the ethyl acetate layer is taken. The organic layer is successively washed with water and brine, dried over magnesium sulfate, and concentrated in vacuo. The residue is purified by silica gel column chromatography (toluene:ethyl acetate=4:1) to give (2S,4S)-1-p-methoxybenzyloxycarbonyl-4-tritylthio-2-(N-p-methoxybenzyloxycarbonyl-N-methylaminosulfonylamino)methylpyrrolidine (1.51 g). Yield: 72%. NMR δ($CDCl_3$) ppm: 1.4 to 1.6(m, 1H), 1.9 to 2.1(m, 1H), 2.5 to 3.3(m, 4H), 3.23(s, 3H), 3.5 to 3.8(m, 1H), 3.76(s, 3H), 3.81(s, 3H), 4.93(ABq, J=10.4 Hz, 2H), 5.10(ABq, J=15.2 Hz, 2H), 6.35 to 6.55(m, 1H), 6.8 to 7.5(m, 23H). IR ν ($CHCl_3$) $cm^{-1}$: 1727, 1695.

Step 14. Preparation of a mercapto compound by deprotection

To a solution of (2S,4S)-1-p-methoxybenzyloxycarbonyl-4-tritylthio-2-(N-p-methoxybenzyloxycarbonyl-N-methylaminosulfonyl)aminomethylpyrrolidine (1.5 g: 1.88 mmole) in a mixture of dichloromethane (4 ml) and methanol (10 ml), a solution of pyridine (381 μl: 2.5 eq.) and silver nitrate (640 mg: 2 eq.) in water (6 ml) is added with stirring under ice cooling. The mixture is stirred at the same temperature for 30 minutes. The reaction mixture is diluted with dichloromethane, washed with water, dried over magnesium sulfate, and concentrated in vacuo to about 5 ml. The residue is dissolved in methanol (10 ml) and hydrogen sulfide is bubbled through it. The mixture freed from solid by filtering is concentrated in vacuo. The residue is purified by silica gel column chromatography (toluene:ethyl acetate=2:1) to give (2S,4S)-1-p-methoxybenzyloxycarbonyl-4-mercapto-2-(N-p-methoxybenzyloxycarbonyl-N-methylaminosulfonyl)aminomethylpyrrolidine (866 mg). Yield: 83%. NMR δ($CDCl_3$) ppm: 1.6 to 1.8(m, 1H), 2.3 to 2.6(m, 1H), 2.9 to 3.4(m, 5H), 3.3(s, 3H), 3.8(s, 6H), 3.8 to 4.2(m, 1H), 6.3 to 6.6(m, 1H), 6.88(d, J=8.6 Hz, 2H), 7.2 to 7.4(m, 2H). IR ν ($CHCl_3$) $cm^{-1}$: 1690.

## PEPARATIVE EXAMPLE 2 OF A PYRROLIDINE DERIVATIVE

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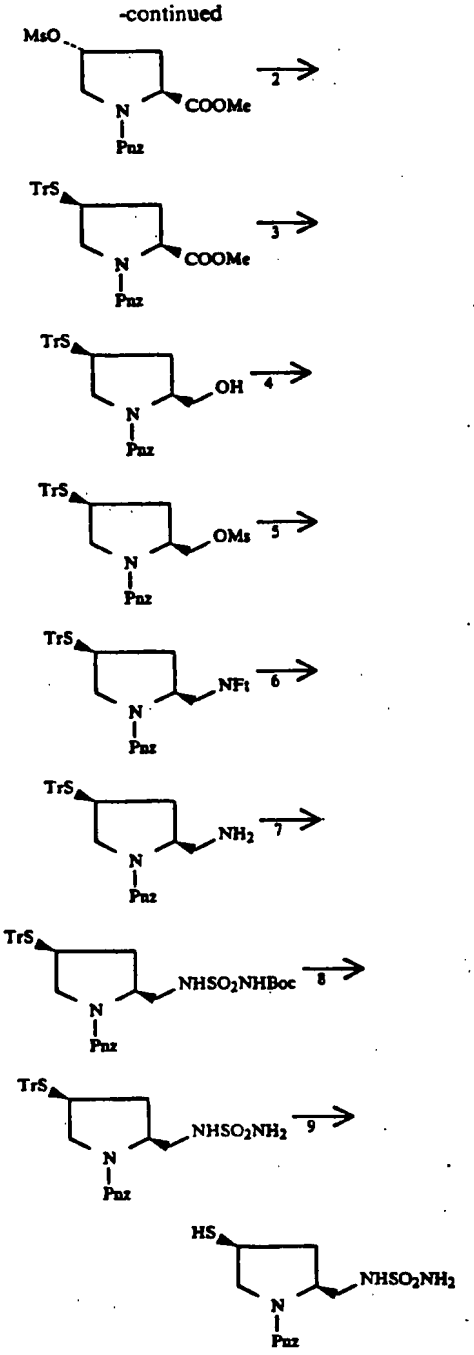



Step 1 Preparation of an O-mesyl compound

To a solution of (2S,4R)-1-p-nitrobenzyloxycarbonyl-4-hydroxypyrrolidine-2-carboxylic acid methyl ester (59.44 g: 0.183 mole) in dichloromethane (150 ml) stirring at −20° C., triethylamine (30.5 ml: 1.2 eq.) and methanesulfonyl chloride (17 ml: 1 eq.) are added. The mixture is stirred at the same temperature for 35 minutes. To the mixture is added ice water and ethyl acetate. The organic layer is taken, washed with water, dried over magnesium sulfate, and concentrated in vacuo to give (2S,4R)-1-p-nitrobenzyloxycarbonyl-4-

methanesulfonyloxypyrrolidine-2-carboxylic acid methyl ester (74.05 g). Yield: Quantitative. NMR δ($CDCl_3$) ppm: 2.20 to 2.42(m, 1H), 2.55 to 2.85(m, 1H), 3.07(s, 3H), 3.67(s, 1.5H), 3.78(s, 1.5H), 3.80 to 4.05(m, 2H), 4.53(t, J=7 Hz, 1H), 5.06 to 5.40(m, 3H), 7.47(d, J=9 Hz, 1H), 7.51(d, J=9 Hz, 1H), 8.23(d, J=9 Hz, 2H). IR ν ($CHCl_3$) $cm^{-1}$: 1748, 1712, 1608.

Step 2. Preparation of a tritylthio compound

To a solution of tritylmercaptan (37.69 g: 1.5 eq.) in tetrahydrofuran (180 ml), an oil suspension containing 60% sodium hydride (4.73 g: 1.3 eq.) is added with stirring at 0° C. The mixture is stirred at room temperature overnight. A solution of (2S,4R)-1-p-nitrobenzyloxycarbonyl-4-methanesulfonyloxypyrrolidine-2-carboxylic acid methyl ester (36.58 g: 90.9 mmole) in tetrahydrofuran (180 ml) is added to the reaction mixture with stirring at 0° C., and the mixture is stirred at 60° C. for 30 minutes. The reaction mixture is poured into cold dilute hydrochloric acid and extracted with ethyl acetate. The extract is successively washed with water and brine, dried, and concentrated in vacuo. The residue is purified by silica gel column chromatography (toluene:ethyl acetate=9:1 to 4:1) to give (2S,4S)-1-p-nitrobenzyloxycarbonyl-4-tritylthiopyrrolidine-2-carboxylic acid methyl ester (25.48 g). Yield: 48.1%. NMR δ($CDCl_3$) ppm: 1.63 to 2.35(m, 2H), 2.68 to 3.50(m, 3H), 3.60(s, 1.5H), 3.72(s, 1.5H), 4.02 to 4.15(m, 1H), 4.95 to 5.28(m, 2H), 7.10 to 7.52(m, 17H), 8.17(d, J=9 Hz, 1H), 8.24(d, J=9 Hz, 1H). IR ν ($CHCl_3$) $cm^{-1}$: 1747, 1704, 1607.

Step 3. Preparation of a methylol compound

To a solution of (2S,4S)-1-p-nitrobenzyloxycarbonyl-4-tritylthiopyrrolidine-2-carboxylic acid methyl ester (5 g: 9.01 mmole) in tetrahydrofuran (180 ml) stirring under ice cooling, a solution of sodium borohydride (2.3 g: 1.4 eq.) in ethanol and a solution of lithium chloride (2.76 g: 1.5 eq.) in tetrahydrofuran (60 ml) are added. The mixture is stirred at room temperature for 1 hour. The reaction mixture is poured into a mixture of ice water and ethyl acetate and extracted with ethyl acetate. The extract is successively washed with cold dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and saturated brine, dried over magnesium sulfate, and concentrated in vacuo. The residue is recrystallized from methanol to give (2S,4S)-1-p-nitrobenzyloxycarbonyl-4-tritylthiopyrrolidine-2-methanol (15.9 g). Yield: 65.9%. mp. 122° to 125° C. NMR δ($CDCl_3$) ppm: 1.32 to 1.53(m, 1H), 1.90 to 2.12(m, 1H), 2.65 to 3.05(m, 3H), 3.32 to 3.84(m, 3H), 5.08, 5.17(ABq, J=12 Hz, 2H), 7.08 to 7.55(m, 17H), 8.26(d, J=9 Hz, 2H). IR ν ($CHCl_3$) $cm^{-1}$: 3400br, 1681, 1607.

Step 4. Preparation of a mesyl compound

To a solution of (2S,4S)-1-p-nitrobenzyloxycarbonyl-4-tritylthiopyrrolidine-2-methanol (5.0 g: 9.01 mmole) in dichloromethane (50 ml) stirring at −15° C., triethylamine (1.63 ml: 1.3 eq.) and methanesulfonyl chloride (0.85 ml: 1.1 eq.) are added. The mixture is stirred at −15° to −10° C. for 30 minutes. The reaction mixture is poured into water and extracted with dichloromethane. The extract is successively washed with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water, dried over magnesium sulfate, and concentrated in vacuo. The residue is purified by silica gel column chromatography (toluene: ethyl acetate=9:1) to give (2S,4S)-1-p-nitrobenzyloxycarbonyl-4-tritylthiopyrrolidine-2-methanol methanesulfonate (4.86 g). Yield: 85.2%. NMR δ($CDCl_3$) ppm: 1.65 to 1.93(m, 1H), 2.00 to 2.26(m, 1H), 2.68 to 2.92(m, 3H), 2.96(s, 3H), 3.78 to 3.98(m, 1H), 4.16 to 4.30(m, 1H), 4.38 to 4.52(m, 1H), 5.11(br s, 2H), 7.08 to 7.52(m, 17H), 8.24(d, J=9 Hz, 2H). IR ν ($CHCl_3$) $cm^{-1}$: 1699, 1606.

Step 5. Preparation of a phthalimido compound

A solution of (2S,4S)-1-p-nitrobenzyloxycarbonyl-4-tritylthiopyrrolidine-2-methanol methanesulfonate (4.39 g: 6.93 mmole) and potassium phthalimide (2.57 g: 2 eq.) in dimethylformamide (30 ml) is stirred at 70° C. for 6 hours. The reaction mixture is poured into ice water and the precipitate is filtered off. The precipitate is dissolved in ethyl acetate, washed with saturated brine, dried over magnesium sulfate, and concentrated in vacuo. The residue is purified by silica gel column chromatography (toluene:ethyl acetate) to give (2S,4S)-1-p-nitrobenzyloxycarbonyl-2-phthalimidomethyl-4-tritylthiopyrrolidine (3.12 g). Yield: 64.3%. NMR δ($CDCl_3$) ppm: 1.40 to 2.30 (m, 2H), 2.60 to 3.08(m, 2H), 3.10 to 3.40(m, 1H), 3.55 to 4.23(m, 3H), 4.92, 5.06(ABq, J=12 Hz, 2H), 7.08 to 7.50 (m, 17H), 7.60 to 7.82(m, 4H), 8.10(d, J=9 Hz, 1H), 8.19(d, J=9 Hz, 1H). IR ν ($CHCl_3$) $cm^{-1}$: 1720, 1701, 1607.

Step 6. Removal of a phthalyl group

To a solution of (2S,4S)-1-p-nitrobenzyloxycarbonyl-2-phthalimidomethyl-4-tritylthiopyrrolidine (10.46 g: 15.31 mmole) in a mixture of dichloromethane (80 ml) and methanol (160 ml), hydrazine hydrate (1.53 ml: 2 eq.) is added, and the mixture is concentrated to remove dichloromethane by warming and refluxed for 3 hours and 15 minutes. The reaction mixture is concentrated in vacuo. The residue is diluted with dichloromethane and filtered to remove solid. The filtrate is washed with water, dried over magnesium sulfate, and concentrated in vacuo to give crude (2S,4S)-1-p-nitrobenzyloxycarbonyl-2-aminomethyl-4-tritylthiopyrrolidine (7.71 g). Yield: 91%. NMR δ($CDCl_3$:$CD_3OD$=2:1) ppm: 1.46 to 3.76(m, 10H), 5.04, 5.12(ABq, J=15 Hz, 2H), 7.10 to 7.56(m, 17H), 8.12 to 8.30(m, 2H). IR ν ($CHCl_3$) $cm^{-1}$: 1695, 1606.

Step 7. Preparation of an N-sulfamoyl compound

A solution of (2S,4S)-1-p-nitrobenzyloxycarbonyl-2-aminomethyl-4-tritylthiopyrrolidine (4.7 g: 8.49 mmole) is dissolved in dichloromethane (435 ml) and cooled to a temperature of −70° C. To the mixture, a solution of diisopropylethylamine (3.4 ml: 2.3 eq.) and 1M t-butoxycarbonylaminosulfonyl chloride (prepared from chlorosulfonyl isocyanate and t-butanol before hand) in dichloromethane (21 ml), and the mixture is stirred for 1 hour and diluted with ice water. The reaction mixture is successively washed with dilute hydrochloric acid and aqueous sodium hydrogen carbonate, dried over magnesium sulfate, and concentrated. The residue is purified by silica gel column chromatography (toluene:ethyl acetate) to give (2S,4S)-1-p-nitrobenzyloxycarbonyl-2-t-butoxycarbonyl-aminosulfonylaminomethyl-4-tritylthiopyrrolidine (1.49 g). Yield: 24%. NMR δ($CDCl_3$) ppm: 1.40 to 2.30(m, 2H), 1.44(s, 9H), 2.60 to 3.40(m, 5H), 3.71 to 3.95(m, 1H), 5.08, 5.13(ABq, J=12 Hz, 2H), 6.27(br s, 1H), 7.07 to 7.55(m, 17H), 8.21(d, J=7 Hz, 1H), 8.26(d, J=7 Hz, 1H). IR ν ($CHCl_3$) $cm^{-1}$: 3390, 1737, 1695, 1606.

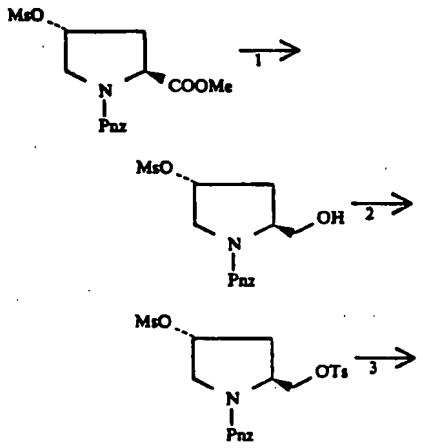
Step 8. Removal of a Boc group

To a solution of (2S,4S)-1-p-nitrobenzyloxycarbonyl-2-t-butoxycarbonylaminosulfonylaminomethyl-4-tritylthiopyrrolidine (1.46 g: 2 mmole) in dichloromethane (5 ml) under ice cooling, anisole (2.4 ml) and trifluoroacetic acid (3.9 ml) are added. The mixture is stirred at room temperature for 2 hours. The reaction mixture is diluted with ethyl acetate and ice water and extracted with ethyl acetate. The extract is successively washed with water and saturated brine, dried over magnesium sulfate, and concentrated in vacuo. The residue is recrystallized from n-hexane to give (2S,4S)-1-p-nitrobenzyloxycarbonyl-2-sulfamoylaminomethyl-4-tritylthiopyrrolidine (1.4 g). Yield: Nearly quantitative. NMR $\delta(CDCl_3)$ ppm: 1.43 to 1.70(m, 1H), 2.08 to 2.30(m, 1H), 2.65 to 3.50(m, 5H), 3.74 to 4.00(m, 1H), 5.03, 5.13(ABq, J=15 Hz, 2H), 5.73(br s, 1H), 7.00 to 7.60(m, 17H), 8.25(d, J=9Hz, 2H). IR $\nu$ ($CHCl_3$) $cm^{-1}$: 3334br, 1688, 1607.

Step 9. Preparation of a mercapto compound by deprotection

To a solution of (2S,4S)-1-p-nitrobenzyloxycarbonyl-2-sulfamoylaminomethyl-4-tritylthiopyrrolidine (668 mg: 0.95 mmole) in tetrahydrofuran (6 ml), a solution of pyridine (0.254 ml: 2.7 eq.) and silver nitrate (403 mg: 2.5 eq.) in water (2 ml) is added under ice cooling. The mixture is stirred at room temperature for 1 hour. The reaction mixture is diluted with dichloromethane (3 ml) and methanol (3 ml), and hydrogen sulfide is bubbled through it under ice cooling for 10 minutes. The resulting precipitate is removed by filtering. The filtrate is diluted with dichloromethane, washed with water, dried over magnesium sulfate, and concentrated in vacuo. The residue is purified by silica gel column chromatography (toluene: ethyl acetate) to give (2S,4S)-1-p-nitrobenzyloxycarbonyl-2-sulfamoylaminomethyl-4-mercaptopyrrolidine (233 mg). Yield: 63%. NMR $\delta(CDCl_3$-$CD_3OD)$ ppm: 1.42(t, J=7 Hz, 1H), 1.65 to 1.93(m, 1H), 2.48 to 2.70(m, 1H), 3.05 to 3.63(m, 4H), 3.93 to 4.16(m, 2H), 5.22(s, 2H), 7.53(d, J=8 Hz, 2H), 8.23(d, J=8 Hz, 2H). IR $\nu$ ($CHCl_3$) $cm^{-1}$: 3276br, 1692, 1607.

PREPARATIVE EXAMPLE 3 OF A PYRROLIDINE DERIVATIVE

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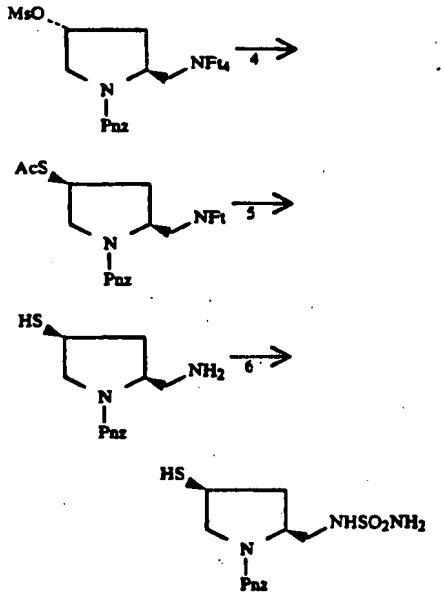



Step 1. Preparation of a methylol compound

To a solution of (2S,4R)-1-p-nitrobenzyloxycarbonyl-4-methanesulfonyloxypyrrolidine-2-carboxylic acid methyl ester (79.4 g: 0.197 mmole) in a mixture of ethanol (300 ml) and tetrahydrofuran (150 ml), sodium borohydride (10.44 g: 1.4 eq.) is added in small portions with stirring at 0° C. The mixture is stirred at 0° C. for 1.5 hours and at room temperature for 5 hours. To the reaction mixture under ice cooling, 5N-hydrochloric acid (100 ml) is added. The mixture is diluted with water, and extracted with ethyl acetate. The extract is washed with brine, dried over sodium sulfate, and concentrated in vacuo. The residue is recrystallized from a mixture of dichloromethane and ether to give (2S,4R)-1-p-nitrobenzyloxycarbonyl-4-methanesulfonyloxypyrrolidine-2-methanol (51.9 g). Yield: 70%. NMR $\delta(CDCl_3)$ ppm: 1.93 to 2.14(m, 1H), 2.32 to 2.48(m, 1H), 3.06(s, 3H), 3.53 to 4.28(m, 6H), 5.26(s, 2H), 7.53(d, J=9 Hz, 2H), 8.24(d, J=9 Hz, 2H). IR $\nu$ ($CHCl_3$) $cm^{-1}$: 3404, 1698, 1607.

Step 2. Preparation of a tosyl compound

To a solution of (2S,4R)-1-p-nitrobenzyloxycarbonyl-4-methanesulfonyloxypyrrolidine-2-methanol (28.8 g: 77 mmole) in dichloromethane (150 ml) under ice cooling, p-toluenesulfonyl chloride (19.11 g: 1.3 eq.), triethylamine (10.4 ml: 1.3 eq.) and dimethylaminopyridine (0.94 g: 0.1 eq.) are added. The mixture is stirred at 25° C. for 7 hours. The reaction mixture is diluted with ice water. The resultant organic layer is taken, successively washed with aqueous sodium hydrogen carbonate and water, dried over magnesium sulfate, and concentrated in vacuo. The residue is recrystallized from n-hexane to give (2S,4R)-1-p-nitrobenzyloxycarbonyl-4-methanesulfonyloxypyrrolidine-2-methanol p-toluenesulfonate (37.7 g). Yield: 93%. NMR $\delta(CDCl_3)$ ppm: 2.20 to 2.50(m, 1H), 2.44(s, 3H), 3.05(s, 3H), 3.45 to 4.60(m, 5H), 5.18(s, 2H), 5.26(br s, 1H), 7.34(d, J=8 Hz, 2H), 7.50(d, J=8 Hz, 2H), 7.75(d, J=8 Hz, 2H), 8.23(d, J=8 Hz, 2H). IR $\nu$ ($CHCl_3$) $cm^{-1}$: 1700, 1599.

Step 3. Preparation of a phthalimido compound

A mixture of (2S,4R)-1-p-nitrobenzyloxycarbonyl-4-methanesulfonyloxypyrrolidine-2-methanol p-toluenesulfonate (25 g: 47.3 mmole) and potassium phthalimide (17.52 g: 2 eq.) in dimethylformamide (250 ml) is stirred at 60° C. for 7 hours. The reaction mixture is poured into ice water and filtrated. The resulting precipitate is dissolved in ethyl acetate, washed with saturated brine, dried over magnesium sulfate, and concentrated in vacuo. The residue is recrystallized from methanol to give (2S,4R)-1-p-nitrobenzyloxycarbonyl-2-phthalimidomethyl-4-methanesulfonyloxypyrrolidine (18.76 g). Yield: 79%. mp. 121° to 123° C. NMR $\delta(CDCl_3)$ ppm: 2.03 to 2.60(m, 2H), 3.02(s, 3H), 3.50 to 4.15(m, 4H), 4.40 to 4.63(m, 1H), 5.10, 5.29(ABq, J=15 Hz, 2H), 5.10 to 5.30(m, 1H), 7.46 (d, J=9 Hz, 1H), 7.57(d, J=9 Hz, 1H), 7.63 to 7.88(m, 4H), 8.20(d, J=9 Hz, 2H) IR $\nu$ ($CHCl_3$) $cm^{-1}$: 1773, 1715, 1605.

Step 4. Preparation of an acetylthio compound

A solution of (2S,4R)-1-p-nitrobenzyloxycarbonyl-2-phthalimidomethyl-4-methanesulfonyloxypyrrolidine (10 g: 19.88 mmole) and potassium thioacetate (4.54 g: 2 eq.) in dimethylformamide (60 ml) is stirred at 60° C. for 3 hours. The reaction mixture is poured into ice water (200 ml) and filtered. The precipitate is dissolved in ethyl acetate, dried over magnesium sulfate, and concentrated in vacuo. The residue is purified by silica gel column chromatography (toluene: ethyl acetate) to give (2S,4S)-1-p-nitrobenzyloxycarbonyl-2-phthalimidomethyl-4-acetylthiopyrrolidine (8.7 g). Yield: 90%. NMR $\delta(CDCl_3)$ ppm: 1.65 to 1.97(m, 1H), 2.47 to 2.67(m, 1H), 3.24 to 3.34(q, 1H), 3.73 to 4.24(m, 4H), 4.30 to 4.54(m, 1H), 5.02(dd, J=14 Hz, J=7 Hz, 1H), 5.20(d, J=14 Hz, 1H), 7.42(d, J=9 Hz, 1H), 7.45(d, J=9 Hz, 1H), 7.60 to 8.86(m, 4H), 8.17(d, J=9 Hz, 2H). IR $\nu$ ($CHCl_3$) $cm^{-1}$: 1773, 1714, 1605.

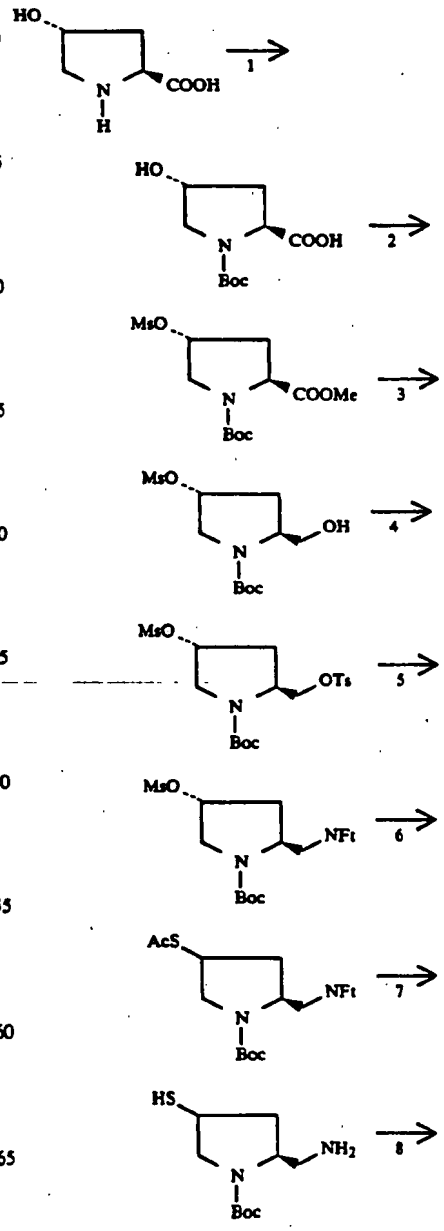
Step 5. Removal of a phthalyl and an acetyl groups

To a solution of (2S,4S)-1-p-nitrobenzyloxycarbonyl-2-phthalimidomethyl-4-acetylthiopyrrolidine (4.92 g: 10.18 mmole) in a mixture of dichloromethane (15 ml) and methanol (75 ml), hydrazine hydrate (1.53 ml: 3 eq.) is added. The mixture is warmed to removed dichloromethane and heated to reflux for 1 hour and 10 minutes. The reaction mixture is concentrated in vacuo. The residue is diluted with dichloromethane and filtered. The filtrate is washed with water, dried over magnesium sulfate, and concentrated in vacuo to give crude (2S,4S)-1-p-nitrobenzyloxycarbonyl-2-aminomethyl-4-mercaptopyrrolidine (3.3 g). Yield: Quantitative. NMR $\delta(CDCl_3)$ ppm: 1.63 to 1.90(m, 1H), 2.48 to 2.68(m, 1H), 2.86 to 3.43(m, 4H), 3.65 to 4.23(m, 2H), 5.22(s, 2H), 7.52(d, J=9 Hz, 2H), 8.23 (d, J=9 Hz, 2H).

Step 6. Preparation of an N-sulfamoyl compound

To a solution of crude (2S,4S)-1-p-nitrobenzyloxycarbonyl-2-aminomethyl-4-mercaptopyrrolidine (3.3 g: 10.18 mmole) in dichloromethane (100 ml) at −78° C., triethylamine (2.84 ml: 2.2 eq.) and trimethylchlorosilane (3.12 ml: 2.2 eq.) are dropwise added. After stirring for 20 minutes, triethylamine (4.25 ml: 3 eq.) and 1M-sulfamoyl chloride in dichloromethane (25 ml: 2.5 eq.) are dropwise added to the mixture. After 20 minutes stirring, the reaction mixture is acidified with hydrochloric acid, warmed to room temperature, and extracted with dichloromethane. The extract is washed with water, and 1N-hydrochloric acid (10 ml) and methanol (30 ml) are added thereto. The solution is stirred at room temperature for 30 minutes. The reaction mixture is washed with water, dried over magnesium sulfate, and concentrated in vacuo. The residue is purified by silica gel column chromatography (toluene: ethyl acetate) to give (2S,4S)-1-p-nitrobenzyloxycarbonyl-2-sulfamoylaminomethyl-4-mercaptopyrrolidine (2.65 g). Yield: 66.7%. NMR $\delta(CDCl_3$-$CD_3OD)$ ppm: 1.42(t, J=7 Hz, 1H), 1.65 to 1.93(m, 1H), 2.48 to 2.70(m, 1H), 3.05 to 3.63(m, 4H), 3.93 to 4.16(m, 2H), 5.22(s, 2H), 7.53(d, J=8 Hz, 2H), 8.23(d, J=8 Hz, 2H). IR $\nu$ ($CHCl_3$) $cm^{-1}$: 3276br, 1692, 1607.

PREPARATIVE EXAMPLE 4 OF A PYRROLIDINE DERIVATIVE



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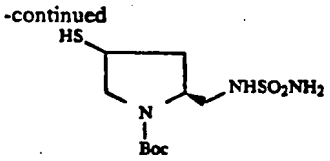


Step 1. Preparation of a Boc compound

To a suspension of trans-4-hydroxy-L-proline (50 g) in a mixture of water (300 ml) and t-butanol (100 ml) are added aqueous sodium hydrogen carbonate (32.3 g), di-t-butyl dicarbonate (104 g) and dioxane (200 ml). The mixture is stirred at room temperature overnight. The organic solvent is removed and the resulting aqueous solution is layered with methyl ethyl ketone and ethyl acetate, and acidified with conc. hydrochloric acid (34.5 ml) under ice cooling. The organic layer is taken, washed with saturated brine, dried over sodium sulfate, and concentrated in vacuo. The residue is recrystallized from ethyl acetate-toluene to give trans-1-t-butoxycarbonyl-4-hydroxy-L-proline (82.9 g). Colorless crystals. Yield: 94%. mp. 126° to 128° C. NMR $\delta(CDCl_3)$ ppm: 1.43, 1.46(2×s, 9H), 1.95 to 2.36(m, 2H), 3.36 to 3.6(m, 2H), 4.23 to 4.44(m, 2H). IR $\nu$ ($CHCl_3$) $cm^{-1}$: 3360, 1735, 1656.

Elemental analysis ($C_{10}H_{17}NO_5$) Calcd.: C, 51.94; H, 7.41; N, 6.06. Found: C, 51.65; H, 7.38; N, 5.99.

Step 2. Preparation of a compound having mesyloxy and methoxycarbonyl groups

To a solution of trans-1-t-butoxycarbonyl-4-hydroxy-L-proline (8.5 g) in tetrahydrofuran (110 ml) at −30° C., triethylamine (12.8 ml) and methanesulfonyl chloride (6.27 ml) are added. The mixture is stirred at the same temperature for 30 minutes. To the mixture triethylamine (5.13 ml) and methanol (30 ml) are added. The mixture is stirred for 30 minutes. The reaction mixture is acidified with 1N-hydrochloric acid (37 ml) and extracted with ethyl acetate. The extract is successively washed with water, aqueous sodium hydrogen carbonate, water and saturated brine, dried over sodium sulfate, and concentrated in vacuo. The residue is purified by silica gel column chromatography and recrystallized from toluene-petroleum ether to give (2S,4R)-1-t-butoxycarbonyl-4-methanesulfonyloxypyrrolidine-2-carboxylic acid methyl ester (9.16 g). Colorless crystals. Yield: 77%. mp. 86° to 87° C. NMR $\delta(CDCl_3)$ ppm: 1.42, 1.47, 1.50(3×s, 9H), 2.19 to 2.35(m, 1H), 2.48 to 2.75(m, 1H), 3.06, 3.07, 3.26(3×s, 3H), 3.59 to 4.12(m, 5H), 4.35 to 4.60(m, 1H), 5.18 to 5.32(m, 1H). IR $\nu$ ($CHCl_3$) $cm^{-1}$: 1748, 1698.

Step 3. Preparation of a methylol compound

To a solution of (2S,4R)-1-t-butoxycarbonyl-4-methanesulfonyloxypyrrolidine-2-carboxylic acid methyl ester (8.11 g) in tetrahydrofuran (49 ml) stirring under ice cooling, sodium borohydride (2.36 g) and methanol (20 ml) are added. The mixture is stirred at room temperature for 25 minutes and at 60° C. for 25 minutes. The mixture is cooled with ice and filtered. The filtrate is concentrated, diluted with ethyl acetate, washed with water, dried over sodium sulfate, and concentrated in vacuo. The residue is recrystallized from petroleum ether-ether to give (2S,4R)-1-t-butoxycarbonyl-4-methanesulfonyloxypyrrolidine-2-methanol (5.96 g). Colorless crystals. Yield: 80%. mp. 95° to 96° C. NMR $\delta(CDCl_3)$ ppm: 1.48(s, 9H), 1.78 to 2.02(m, 1H), 2.3 to 2.48(m, 1H), 3.05(s, 3H), 3.5 to 3.65(m, 2H), 3.65 to 4.0(m, 2H), 4.03 to 4.25(m, 1H), 5.2(s, 1H). IR $\nu$ ($CHCl_3$) $cm^{-1}$: 3460, 1680.

Step 4. Preparation of a tosyl compound

To a solution of (2S,4R)-1-t-butoxycarbonyl-4-methanesulfonyloxypyrrolidine-2-methanol (12.0 g) in dichloromethane (180 ml) stirring under ice cooling, triethylamine (6.23 ml), p-toluenesulfonyl chloride (8.52 g) and N,N-dimethylaminopyridine (993 mg) are successively added. The mixture is heated to reflux for 3 hours, supplemented with triethylamine (0.57 ml) and p-toluenesulfonyl chloride (775 mg), and heated to reflux for 1 hour. The reaction mixture is acidified with dilute hydrochloric acid. The organic layer is taken, washed with water, dried over sodium sulfate and concentrated in vacuo. The residue is purified by silica gel column chromatography and recrystallized from n-hexane to give (2S,4R)-1-t-butoxycarbonyl-4-methanesulfonyloxypyrrolidine-2-methanol p-toluenesulfonate (16.8 g). Yield: 92%. mp. 65° to 66° C. NMR $\delta(CDCl_3)$ ppm: 1.42(s, 9H), 2.15 to 2.55(m, 2H), 2.45(s, 3H), 3.03(s, 3H), 3.3 to 4.5(m, 5H), 5.1 to 5.25(m, 1H), 7.35(d, $J$=8.0 Hz, 2H), 7.76(d, $J$=8.0 Hz, 2H). IR $\nu$ ($CHCl_3$) $cm^{-1}$: 1693.

Step 5. Preparation of a phthalimido compound

To a solution of (2S,4R)-1-t-butoxycarbonyl-4-methanesulfonyloxypyrrolidine-2-methanol p-toluenesulfonate (20.78 g) in dimethylformamide (200 ml), potassium phthalimide (9.61 g) is added. The mixture is stirred at 70° C. for 3 hours. The reaction mixture is poured into a mixture of water and ethyl acetate. The organic layer is taken, successively washed with dilute aqueous sodium hydroxide and water, dried over sodium sulfate, and concentrated in vacuo. The residue is purified by 5% wet silica gel column chromatography to give (2S,4R)-1-t-butoxycarbonyl-2-phthalimidomethyl-4-methanesulfonyloxypyrrolidine (11.17 g). Yield: 60%. Colorless foam. NMR $\delta(CDCl_3)$ ppm: 1.33, 1.42(2×s, 9H), 2.0 to 2.55(m, 2H), 3.02(s, 3H), 3.4 to 4.6(m, 5H), 5.15 to 5.3(m, 1H), 7.6 to 7.95(m, 4H). IR $\nu$ ($CHCl_3$) $cm^{-1}$: 1775, 1716, 1693.

Step 6. Preparation of an acetylthio compound

To a solution of (2S,4R)-1-t-butoxycarbonyl-2-phthalimidomethyl-4-methanesulfonyloxypyrrolidine (3 g) in dimethylformamide (30 ml), potassium thioacetate (1.65 g) is added. The mixture is stirred at 60° C. for 3.5 hours. The reaction mixture is poured into a mixture of ethyl acetate and dilute hydrochloric acid. The organic layer is taken, washed with water, dried over sodium sulfate, and concentrated in vacuo. The residue is purified by silica gel column chromatography to give (2S,4S)-1-t-butoxycarbonyl-2-phthalimidomethyl-4-acetylthiopyrrolidine (2.12 g). Yield: 74%. Orange colored syrup. NMR $\delta(CDCl_3)$ ppm: 1.30, 1.39(2×s, 9H), 1.6 to 2.0(m, 1H), 2.34(s, 3H), 2.4 to 2.67(m, 1H), 3.15 to 3.3(m, 1H), 3.65 to 4.55(m, 5H), 7.6 to to 8.0(m, 4H). IR $\nu$ ($CHCl_3$) $cm^{-1}$: 1774, 1715, 1688.

Step 7. Removal of a phthalyl and an acetyl groups

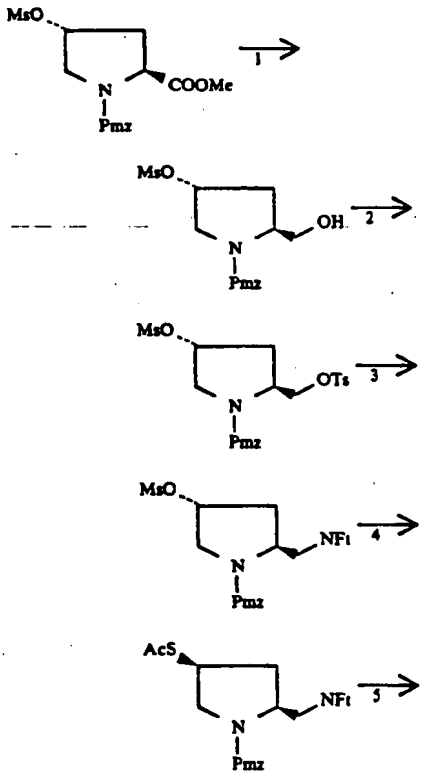
To a solution of (2S,4S)-1-t-butoxycarbonyl-2-phthalimidomethyl-4-acetylthiopyrrolidine (8.58 g) in a mixture of dichloromethane (26 ml) and methanol (129 ml), hydrazine hydrate (4.11 ml) is added. The mixture is heated to reflux for 2 hours and 45 minutes and fil-

tered. The filtrate is concentrated in vacuo. The residue is dissolved in dichloromethane, washed with water, dried over sodium sulfate, and concentrated in vacuo to give crude (2S,4S)-1-butoxycarbonyl-2-aminomethyl-4-mercaptopyrrolidine (4.1 g). Yellow syrup.

Step 8 Preparation of a sulfamoyl compound

To a solution of crude (2S,4S)-1-t-butoxycarbonyl-2-aminomethyl-4-mercaptopyrrolidine (4.1 g) in dichloromethane (250 ml) at −70° C. under a stream of nitrogen, triethylamine (8.87 ml) and trimethylchlorosilane (6.73 ml) are added. The mixture is stirred for 1 hour and 40 minutes, mixed with triethylamine (8.87 ml) and a solution of 1M-sulfamoyl chloride in dichloromethane (64 ml), and stirred for 1 hour. The reaction mixture is acidified with dilute hydrochloric acid. The organic layer is taken, diluted with 1N-hydrochloric acid (21 ml) and methanol (50 ml), stirred for 35 minutes at room temperature, and poured into water. The organic layer is taken, washed with water, dried over magnesium sulfate, and concentrated in vacuo. The residue is purified by silica gel column chromatography to give (2S,4S)-1-t-butoxycarbonyl-2-sulfamoylaminomethyl-4-mercaptopyrrolidine (4.57 g). Yield: 69%. Colorless syrup. NMR δ($CDCl_3$) ppm: 1.46(s, 9H), 1.5 to 1.8(m, 1H), 1.71(d, J=6.6 Hz, 1H), 2.5 to 2.67(m, 1H), 3.0 to 3.46(m, 4H), 3.85 to 4.2(m, 2H), 4.6 (br s, 2H). IR ν ($CHCl_3$) $cm^{-1}$: 3420, 3340, 3270, 1679.

## PREPARATIVE EXAMPLE 5 OF A PYRROLIDINE DERIVATIVE

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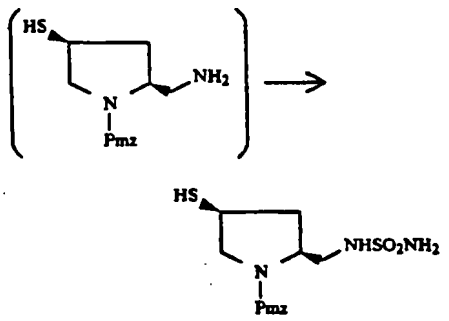



Step. 1 Preparation of a methylol compound

To a solution of (2S,4R)-1-p-methoxybenzyloxycarbonyl-4-methanesulfonyloxypyrrolidine-2-carboxylic acid methyl ester (79.4 g: 205 mmole) in a mixture of tetrahydrofuran (200 ml) and ethanol (300 ml), sodium borohydride (14 g) is added in several portions under ice cooling. The mixture is stirred at room temperature for 4 hours. The reaction mixture is neutralized with conc. sulfuric acid, concentrated in vacuo to approximately a half volume, diluted with water, and extracted with ethyl acetate. The extract is successively washed with aqueous sodium hydrogen carbonate, water and brine, dried over magnesium sulfate, and concentrated in vacuo. The residue is purified by silica gel column chromatography (toluene:ethyl acetate=1:2) to give (2S,4R)-1-p-methoxybenzyloxycarbonyl-4-methanesulfonyloxypyrrolidine-2-methanol (58.7 g). Yield: 81.7%. NMR δ($CDCl_3$) ppm: 1.8 to 2.2(m, 1H), 2.3 to 2.5(m, 1H), 3.01(s, 3H), 3.57 (d, J=4.4 Hz, 1H), 3.64(d, J=4.4 Hz, 1H), 3.81(s, 3H), 3.82 to 4.3(m,3H), 5.09(s, 2H), 5.21(br s, 1H), 6.89(d, J=8.8 Hz, 2H), 7.31(d, J=8.8 Hz,2H).

Step 2. Preparation of a tosyl compound

To a solution of (2S,4R)-1-p-methoxybenzyloxycarbonyl-4-methanesulfonyloxypyrrolidine-2-methanol (8.7 g: 24.2 mmole) in dichloromethane(80 ml) are added triethylamine (4.05 ml), p-toluenesulfonyl chloride (5.08 g) and 4-dimethylaminopyridine (148 mg). The mixture is stirred at room temperature overnight. The reaction mixture is washed with water and brine, dried over magnesium sulfate, and concentrated in vacuo. The residue is purified by silica gel column chromatography (toluene:ethyl acetate=1:1) to give (2S,4R)-1-p-methoxybenzyloxycarbonyl-4-methanesulfonyloxypyrrolidine-2-methanol p-toluenesulfonate (11.75 g). Yield: 95%. NMR δ($CDCl_3$) ppm: 2.2 to 2.5(m), 2.44(s, 3H), 2.98(s, 3H), 3.4 to 3.6(m, 2H), 3.82(s, 3H), 3.8 to 4.6(m), 5.03, 4.95(ABq, J=12 Hz, 2H), 5.2 (br s, 1H), 6.89(d, J=8.6 Hz, 2H), 7.18 to 7.4(m, 4H), 7.6 to 7.8(m, 2H). IR ν ($CHCl_3$) $cm^{-1}$: 1698, 1612.

Step 3. Preparation of a phthalimido compound

To a solution of (2S,4R)-1-p-methoxybenzyloxycarbonyl-4-methanesulfonyloxypyrrolidine-2-methanol p-toluenesulfonate (6.35 g: 12.27 mmole) in dimethylformamide (60 ml), potassium phthalimide (2.7 g) is added. The mixture is stirred at 70° C. for 4 hours. The reaction mixture is poured into ice water and extracted with ethyl acetate. The extract is successively washed with water and brine, dried over magnesium sulfate,

and concentrated in vacuo. The residue is purified by silica gel column chromatography (toluene:ethyl acetate=2:1) to give (2S,4R)-1-p-methoxybenzyloxycarbonyl-4-methanesulfonyloxy-2-phthalimidomethylpyrrolidine (4.65 g). Yield: 77.5%. NMR δ($CDCl_3$) ppm: 2 to 2.3(m, 1H), 2.4 to 2.6(m, 1H), 2.95, 2.97(2×s, 3H), 3.43 to 4.2(m, 5H), 3.80(s, 3H), [5.01(s)+5.07, 4.96(ABq, 12.2 Hz), 2H], 5.13 to 5.3(m, 1H). IR ν ($CHCl_3$) $cm^{-1}$: 1774, 1716, 1613.

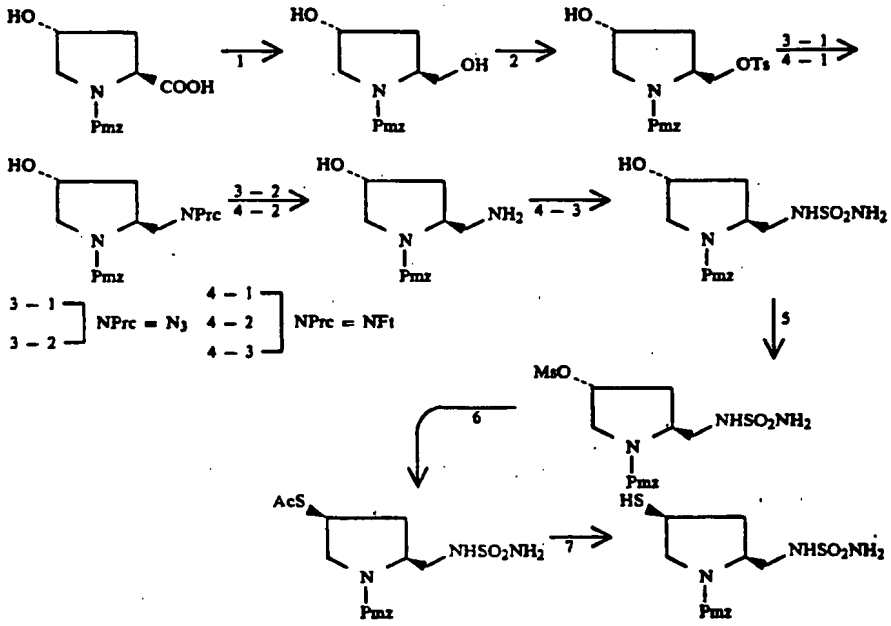
Step 4. Preparation of an acetylthio compound

To a solution of (2S,4R)-1-p-methoxybenzyloxycarbonyl-4-methanesulfonyloxy-2-phthalimidopyrrolidine (4.0 g: 8.19 mmole) in dimethylformamide (40 ml), potassium thioacetate (2.1 g) is added. The mixture is stirred at 60° C. for 3 hours. The reaction mixture is diluted with ethyl acetate, successively washed with water and brine, dried over magnesium sulfate, and concentrated in vacuo. The residue is purified by silica gel column chromatography (toluene:ethyl acetate=2:1) to give (2S,4S)-1-p-methoxybenzyloxycarbonyl-4-acetylthio-2-phthalimidomethylpyrrolidine (3.2 g). Yield: 78%. NMR δ($CDCl_3$) ppm: 1.7 to 1.9(m, 1H), 2.4 to 2.7(m, 1H), 3.21, 3.26(2×d, J=7 Hz, 2H), 3.8(s, 3H), 3.7 to 4.2(m), 4.2 to 4.5(m, 1H), [4.95(s)+5.04, 4.83(ABq, J=12 Hz), 2H], 6.83(d, J=7.6 Hz, 2H), 7.18 to 7.3(m, 2H), 7.6 to 7.9(m, 4H). IR ν ($CHCl_3$) $cm^{-1}$: 1773, 1714.

Step 5. Removal of an acetyl and a phthalyl groups and introduction of a sulfamoyl group

To a solution of (2S,4S)-1-p-methoxybenzyloxycarbonyl-4-acetylthio-2-phthalimidomethylpyrrolidine (4.3 g: 9.18 mmole) in a mixture of dichloromethane (13 ml) and methanol (65 ml), hyrazine hydrate (1.78 ml) is added. The mixture is heated to reflux for 4 hours. The reaction mixture is concentrated in vacuo. The residue is dissolved in dichloromethane and filtered under a stream of nitrogen to remove solid. The filtrate is washed with water, dried over magnesium sulfate, and concentrated in vacuo. The resulting residue containing (2S,4S)-1-p-methoxybenzyloxycarbonyl-4-mercapto-2-aminomethylpyrrolidine is diluted with dichloromethane (100 ml), added triethylamine (2.63 g) and trimethylchlorosilane (2.4 ml) at −78° C., and stirred for 20 minutes. To the reaction mixture, triethylamine (2.63 ml) and a solution (16.5 ml) of 1M-sulfamoyl chloride in dichloromethane are added. The mixture is stirred for 20 minutes. The reaction mixture is washed with dilute hydrochloric acid, mixed with 1N-hydrochloric acid (9 ml) and methanol (20 ml), and stirred at room temperature for 30 minutes. The reaction mixture is successively washed with water and brine, dried over magnesium sulfate, and concentrated in vacuo. The residue is purified by silica gel column chromatography (toluene:ethyl acetate=1:2) to give (2S,4S)-1-p-methoxybenzyloxycarbonyl-4-mercapto-2-sulfamoylaminomethylpyrrolidine (2.71 g). Yield: 78.6%. NMR δ($CDCl_3$) ppm: 1.6 to 2.0(m, 2H), 2.4 to 2.7(m, 1H), 3.1 to 3.8(m,4H), 3.81(s, 3H), 3.9 to 4.2(m, 2H), 4.6 to 5.0(m, 2H), 5.04(s, 2H), 5.97(br s, 1H), 6.89(d, J=8.6 Hz, 2H), 7.30(d, J=8.6 Hz, 2H). IR ν ($CHCl_3$) $cm^{-1}$: 3668, 3424, 1683.

## PREPARATIVE EXAMPLE 6 OF A PYRROLIDINE DERIVATIVE




Step 1. Preparation of a methylol compound

To a solution of trans-1-p-methoxybenzyloxycarbonyl-4-hydroxyproline (105.5 g: 357.5 mmole) in tetrahydrofuran (1 liter), triethylamine (54.8 ml) is added. After adding ethyl chloroformate (35.9 ml) dropwise at −30° C., the mixture is stirred for 20 minutes. To the reaction mixture, a solution of sodium borohydride (33.25 g) in water (120 ml) is added dropwise at a temperature in the range of −15° to −5° C., neutralized with conc. hydrochloric acid, and concentrated in vacuo. To the residue, ethyl acetate is added, washed with brine, dried over magnesium sulfate, and concentrated in vacuo to give (2S,4R)-1-p-methoxybenzyloxycarbonyl-4-hydroxypyrrolidine-2-methanol. NMR δ($CDCl_3$) ppm: 1.6 to

1.8(m, 1H), 1.95 to 2.2(m, 1H), 3.4 to 3.8 (m, 4H), 3.8(s, 3H), 4.0 to 4.3(m, 1H), 4.37(br s, 1H), 5.07(s, 2H), 6.88(d, J=8.8 Hz, 2H), 7.30(d, J=8.8 Hz, 2H).

Step 2. Preparation of a tosyl compound

To a solution of (2S,4R)-1-p-methoxybenzyloxycarbonyl-4-hydroxypyrrolidine-2-methanol (64 g: 227.6 mmole) in pyridine (350 ml), p-toluenesulfonyl chloride (48 g) is added. The mixture is stirred at room temperature for 4 hours. The reaction mixture is poured into ice water and extracted with ethyl acetate. The extract is successively washed with water, dilute hydrochloric acid and aqueous sodium hydrogen carbonate, dried over magnesium sulfate, and concentrated in vacuo. The residue is purified by silica gel column chromatography to give (2S,4R)-1-p-methoxybenzyloxycarbonyl-4-hydroxypyrrolidine-2-methanol p-toluenesulfonate (60 g). NMR δ($CDCl_3$) ppm: 2.0 to 2.4(m, 2H), 2.44(s, 3H), 3.3 to 3.7(m, 2H), 3.82(s, 3H), 3.9 to 4.6(m, 4H), 4.8 to 5.1(m, 2H), 6.88(d, J=8.6 Hz, 2H),7.2 to 7.4(m, 4H), 7.6 to 7.8(m, 2H). IR ν ($CHCl_3$) $cm^{-1}$: 3446, 1693.

Step 3. Preparation of an amino precursor (-NProc=azido)

1) To a solution of (2S,4R)-1-p-methoxybenzyloxycarbonyl-4-hydroxypyrrolidine-2-methanol p-toluenesulfonate (8.7 g: 20 mmole) in dimethylformamide (60 ml), a solution of sodium azide (1.56 g) in water (6 ml) is added. The mixture is stirred at 80° C. overnight. The reaction mixture is poured into ice water and extracted with ethyl acetate. The extract is successively washed with water and brine, dried over magnesium sulfate, and concentrated in vacuo to give crude (2S,4R)-1-p-methoxybenzyloxycarbonyl-4-hydroxy-2-azidomethylpyrrolidine (5.6 g). Yield: 92%. NMR δ($CDCl_3$) ppm: 1.95 to 2.1(m, 2H), 3.2 to 3.8(m, 3H), 3.81(s, 3H), 3.83 to 4.6(m, 3H), 5.07(s, 2H), 6.89(d, J=8.8 Hz, 2H), 7.31(d, J=8.8 Hz, 2H). IR ν ($CHCl_3$) $cm^{-1}$: 3420, 2100, 1689.

2) To a solution of the thus obtained (2S,4R)-1-p-methoxybenzyloxycarbonyl-4-hydroxy-2-azidomethylpyrrolidine (5.57 g: 18.18 mmole) in methanol (30 ml) are added, 5% palladium on charcoal (560 mg) and ammonium formate (2.3 g). The mixture is stirred at 45° C. for 2 hours. The reaction mixture is diluted with dichloromethane (50 ml), filtered to remove the catalyst, and concentrated in vacuo. The residue is crystallized from a mixture of dichloromethane and ether and washed with ether to give (2S,4R)-1-p-methoxybenzyloxycarbonyl-4-hydroxy-2-aminomethylpyrrolidine formate (4.28 g). Yield: 72%. NMR δ($CDCl_3$—$CD_3OD$) ppm: 1.6 to 1.82(m, 1H), 2.1 to 2.3(m, 1H), 2.7 to 3.7(m, 4H), 3.81(s, 3H), 4.1 to 4.4(m, 2H), 5.04(s, 2H), 6.88(d, J=8.8 Hz, 2H), 7.28(d, J=8.8 Hz, 2H), 8.47(s, 1H). IR ν ($CHCl_3$) $cm^{-1}$: 3678, 3412, 1678, 1602.

Step 4. Introduction of a protected amino group, removal of the protection, and introduction of a sulfamoyl group (—NProc=phthalimido)

1) To a solution of (2S,4R)-1-p-methoxybenzyloxycarbonyl-4-hydroxypyrrolidine-2-methanol p-toluenesulfonate (24 g: 55.1 mmole) in dimethylformamide (200 ml), potassium phthalimide (15.3 g) is added. The mixture is stirred at 80° C. for 4 hours. The reaction mixture is diluted with ethyl acetate, successively washed with water and brine, dried over magnesium sulfate, and concentrated in vacuo. The residue is purified by silica gel column chromatography (toluene:ethyl acetate=1:2) to give (2S,4R)-1-p-methoxybenzyloxycarbonyl-4-hydroxy-2-phthalimidomethylpyrrolidine (18.1 g). Yield: 80%. NMR δ($CDCl_3$) ppm: 1.9 to 2.2(m, 2H), 3.4 to 4.05(m, 5H), 3.80(s, 3H), 4.3 to 4.6(m, 2H), 4.8 to 5.1(m, 2H), 6.83(d, J=8.2 Hz, 2H), 7.25(d, J=8.2 Hz, 2H), 7.6 to 7.9(m, 4H). IR ν ($CHCl_3$) $cm^{-1}$: 3458, 1773, 1712.

2) To a solution of (2S,4R)-1-p-methoxybenzyloxycarbonyl-4-hydroxy-2-phthalimidomethylpyrrolidine (5.13 g: 12.5 mmole) in a mixture of dichloromethane (15 ml) and methanol (50 ml), hydrazine hydrate (1.0 ml) is added. The mixture is heated to reflux for 2 hours and concentrated in vacuo. The residue is diluted with dichloromethane, filtered to remove solid, washed with brine, dried over magnesium sulfate, and concentrated in vacuo to give a residue containing (2S,4R)-1-p-methoxybenzyloxycarbonyl-4-hydroxy-2-aminomethypyrrolidine as a main component.

3) To a solution of the above-mentioned residue in dichloromethane (70 ml) at −70° C., triethylamine (4.6 ml) and trimethylchlorosilane (3.7 ml) are added. The mixture is stirred for 20 minutes. To the reaction mixture, triethylamine (5.5 ml) and a solution of 1M-sulfamoyl chloride in dichloromethane (34 ml) are added. The mixture is stirred for 15 minutes. The reaction mixture is washed with dilute hydrochloric acid, mixed with methanol (50 ml), and then 4N-hydrochloric acid (3.3 ml) is added under ice cooling. After stirring the mixture, aqueous sodium hydrogen carbonate is added. The organic layer is taken, washed with water and brine, dried over magnesium sulfate, and concentrated in vacuo to give crude (2S,4R)-1-p-methoxybenzyloxycarbonyl-4-hydroxy-2-sulfamoylaminomethylpyrrolidine (3.96 g). NMR δ($CDCl_3$) ppm: 1.8 to 2.25(m, 2H), 3 to 4.5(m, 7H), 3.79(s, 3H), 5.03(s, 2H), 5.2 to 5.8(m, 2H), 6.08(br s, 1H), 6.87(d, J=8.8 Hz, 2H), 7.29(d, J=8.8 Hz, 2H). IR ν ($CHCl_3$) $cm^{-1}$: 3456, 1689.

Step 5 Preparation of a mesyl compound

To a solution of crude (2S,4R)-1-p-methoxybenzyloxycarbonyl-4-hydroxy-2-sulfamoylaminomethylpyrrolidine (1.8 g: 5 mmole) obtained in Step 4 in dichloromethane (20 ml) at −70° C., triethylamine (0.77 ml) and methanesulfonyl chloride (0.39 ml) are added. The mixture is stirred for 45 minutes. The reaction mixture is neutralized with dilute hydrochloric acid, successively washed with water and brine, and concentrated in vacuo to give crude (2S,4R)-1-p-methoxybenzyloxycarbonyl-4-methanesulfonyloxy-2-sulfamoylaminomethylpyrrolidine (2.26 g). NMR δ($CDCl_3$) ppm: 2 to 2.5(m, 2H), 2.99(s, 3H), 3.0 to 4.3(m, 5H), 3.79(s, 3H), 4.8 to 5.3(m, 3H), 5.05(s, 2H), 5.7 to 5.85(m, 1H), 6.88(d, J=8.8 Hz, 2H), 7.29(d, J=8.8 Hz, 2H). IR ν ($CHCl_3$) $cm^{-1}$: 3606, 3416, 1690.

Step 6. Preparation of an acetylthio compound

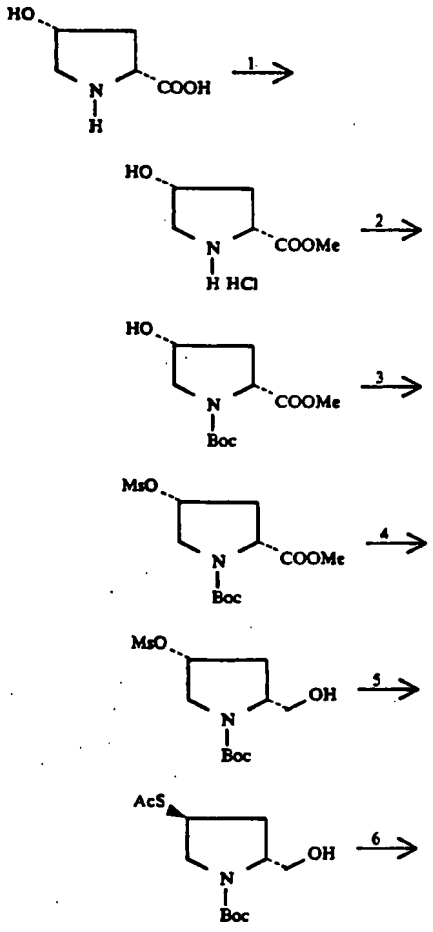
To a solution of crude (2S,4R)-1-p-methoxybenzyloxycarbonyl-4-methanesulfonyloxy-2-sulfamoylaminomethylpyrrolidine (2.26 g) obtained in Step 5 in dimethylformamide (12 ml), potassium thioacetate (1.7 g) is added. The mixture is stirred at 60° C. for 5 hours. The reaction mixture is diluted with ethyl acetate, successively washed with water and brine, dried over magnesium sulfate, and concentrated in vacuo. The residue is purified by silica gel column chromatography (toluene:ethyl acetate=1:2) to give (2S,4S)-1-p-methoxybenzyloxycarbonyl-4-acetylthio-2-sulfamoylaminomethylpyrrolidine (971 mg). NMR δ($CDCl_3$) ppm: 1.8(br s, 1H), 2.33(s, 3H), 2.4 to 2.7(m, 1H), 3.1 to 3.5(m), 3.81(s,

3H), 3.9 to 4.2(m, 2H), 5.05(s, 2H), 6.89(d, J=8.8 Hz, 2H), 7.30(d, J=8.8 Hz, 2H). IR $\nu$ ($CHCl_3$) $cm^{-1}$: 3414, 3276, 1688.

Step 7. Removal of an acetyl group

To a solution of (2S,4S)-1-p-methoxybenzyloxycarbonyl-4-acetylthio-2-sulfamoylaminomethylpyrrolidine (982 mg: 2.35 mmole) in a mixture of dichloromethane (2 ml) and methanol (10 ml), 1N-sodium hydroxide (2.8 ml) is added under ice cooling. The mixture is stirred for 15 minutes. The reaction mixture is diluted with water and extracted with ethyl acetate. The extract is successively washed with water and brine, dried over magnesium sulfate, and concentrated in vacuo. The residue is purified by silica gel column chromatography (toluene:ethyl acetate=1:2) to give (2S,4S)-1-p-methoxybenzyloxycarbonyl-4-mercapto-2-sulfamoylaminomethylpyrrolidine (783 mg). Yield: 89%. NMR $\delta$($CDCl_3$) ppm: 1.6 to 2.0(m, 2H), 2.4 to 2.7(m, 1H), 3.1 to 3.8(m, 4H), 3.81(s, 3H), 3.9 to 4.2(m, 2H), 4.6 to 5.0(m, 2H), 5.04(s, 2H), 5.97(br s, 1H), 6.89(d, J=8.6 Hz, 2H), 7.30(d, J=8.6 Hz, 2H). IR $\nu$ ($CHCl_3$) $cm^{-1}$: 3668, 3424, 1683.

PREPARATIVE EXAMPLE 7-A OF A PYRROLIDINE DERIVATIVE

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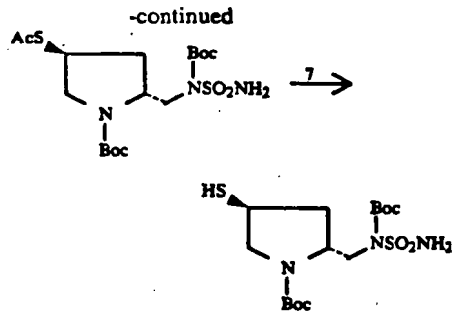



Step A-1. Preparation of an ester compound

To a suspension of cis-4-hydroxy-D-proline (16.46 g: 125.5 mmole) in methanol (66 ml), thionylchloride (9.16 ml: 125.5 mmole) is added in a nitrogen atmosphere under ice cooling, and the mixture is stirred at room temperature for 30 minutes. The mixture is further stirred to react at 40° C. for 4 hours to give (2R,4R)-4-hydroxy-2-methoxycarbonylpyrrolidine hydrochloride as crude crystals (25.74 g). Yield: 113%. Colorless crystals. NMR $\delta$($D_2O$) ppm: 2.3 to 2.6(m, 2H), 3.33(s, 1H), 3.4 to 3.5(m, 2H), 3.84(s, 3H), 4.6 to 4.7(m, 2H). IR $\nu$ (KBr) $cm^{-1}$: 3320, 2980, 1728.

Step A-2. Preparation of a Boc compound

To a suspension of (2R,4R)-4-hydroxy-2-methoxycarbonylpyrrolidine hydrochloride (25.64 g: 125 mmole) in dichloromethane (125 ml), triethylamine (19.11 ml: 137.5 mmole) is added dropwise in a nitrogen atmosphere under ice cooling. The mixture is stirred for 5 minutes at room temperature. Then, a solution of di-t-butyl dicarbonate (34.11 g: 156.3 mmole) in dichloromethane (125 ml) is added dropwise, and the mixture is stirred for 40 minutes at room temperature to give (2R,4R)-1-t-butoxycarbonyl-4-hydroxy-2-methoxycarbonylpyrrolidine (26.85 g). Yield: 88%. Colorless crystals. NMR $\delta$($CDCl_3$) ppm: 1.46(d, J=8.4 Hz, 9H), 2.0 to 2.2(m, 1H), 2.2 to 2.5(m, 1H), 3.4 to 3.8(m, 2H), 3.79(d, J=3.0 Hz, 3H), 4.2 to 4.5(m, 2H). IR $\nu$ (KBr) $cm^{-1}$: 3460, 1730, 1680.

Step A-3. Preparation of a mesyl compound

To a solution of (2R,4R)-1-t-butoxycarbonyl-4-hydroxy-2-methoxycarbonylpyrrolidine (9.81 g: 40 mmole) in dichloromethane (49 ml) in a nitrogen atmosphere under ice cooling, triethylamine (6.67 ml: 48 mmole) and methanesulfonyl chloride (3.70 ml: 48 mmole) are added. The mixture is stirred for 20 minutes to give (2R,4R)-1-t-butoxycarbonyl-4-methanesulfonyloxy-2-methoxycarbonylpyrrolidine as a crude oil (13.05 g). Yield: 101%. NMR $\delta$($CDCl_3$) ppm: 1.46(d, J=9.6 Hz, 9H), 2.5(m, 2H), 3.02(s, 3H), 3.76(s, 3H), 3.8(m, 2H), 4.3 to 4.6(m, 1H), 5.2 to 5.3(m, 1H).

Step A-4. Preparation of a methylol compound

To a solution of (2R,4R)-1-t-butoxycarbonyl-4-methanesulfonyloxy-2-methoxycarbonylpyrrolidine (11.21 g: 34.4 mmole) in a mixture of tetrahydrofuran (34 ml) and ethanol (51 ml), sodium borohydride (5.21 g: 137.7 mmole) is added in a nitrogen atmosphere under ice cooling. The mixture is stirred for 75 minutes at room temperature to give (2R,4R)-1-t-butoxycarbonyl-4-methanesulfonyloxypyrrolidine-2-methanol (8.47 g). Yield: 83%. Colorless crystals. NMR $\delta$($CDCl_3$)

ppm: 1.48(s, 9H), 1.9 to 2.2(m, 1H), 2.3 to 2.5(m, 1H), 3.06 (s, 3H), 3.65(dd, J=11.2 Hz, J=4.0 Hz, 1H), 3.5 to 3.9(m, 2H), 3.84(dd, J=11.2 Hz, J=7.6 Hz, 1H), 4.1(m, 1H), 5.2(m, 1H). IR $\nu$ (KBr) $cm^{-1}$: 3490, 1688.

Step A-5. Preparation of an acetylthio compound

(2R,4R)-1-t-Butoxycarbonyl-4-methanesulfonyloxypyrrolidine-2-methanol (i.e., a substrate) and potassium thioacetate (KSAc) are dissolved in dimethylformamide (DMF), and the mixture is stirred. The conditions for this reaction are shown in Table 1, Step A-5. The reaction mixture is diluted with ethyl acetate, and ice water is added. The organic layer is taken, successively washed with aqueous sodium hydroxide, hydrochloric acid, water and saturated brine, dried over magnesium sulfate, and concentrated in vacuo. The residue is purified by silica gel chromatography to give (2R,4S)-4-acetylthio-1-t-butoxycarbonylpyrrolidine-2-methanol. NMR $\delta(CDCl_3)$ ppm: 1.47(s, 9H), 2.05(t, 2H), 2.34(s, 3H), 3.0 to 3.3(m, 1H), 3.40(dd, J=11.6 Hz, J=5.2 Hz, 1H), 3.5 to 3.9(m, 3H), 3.9 to 4.2(m, 2H).

Step A-6. Introduction of a sulfamide group

a) Production of N-t-butoxycarbonylsulfamide A solution of t-butanol (4.72 ml: 50 mmole) in ethyl acetate (100 ml) is cooled to −40° C., chlorosulfonyl isocyanate (4.35 ml: 50 mmole) is dropwise added thereto, and the mixture is stirred at −18° C. for 20 minutes. The reaction mixture is cooled to −72° C., gaseous ammonia (2 mole) is bubbled with stirring, and the mixture is stirred for 50 minutes while warming up to 10° C. The reaction mixture is acidified with 5N-hydrochloric acid (30 ml) and the formed precipitate is filtered off. The organic layer is taken, successively washed with water and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The crystalline residue is washed with hexane-ethyl acetate (1:5, 90 ml) and recrystallized from ethyl acetate-hexane to give N-t-butoxycarbonylsulfamide (8.81 g). Yield: 89%. Colorless crystals. mp. 130° to 131° C.

NMR $\delta(CD_3SOCD_3)$ ppm: 1.43(s, 9H), 7.27(s, 2H).

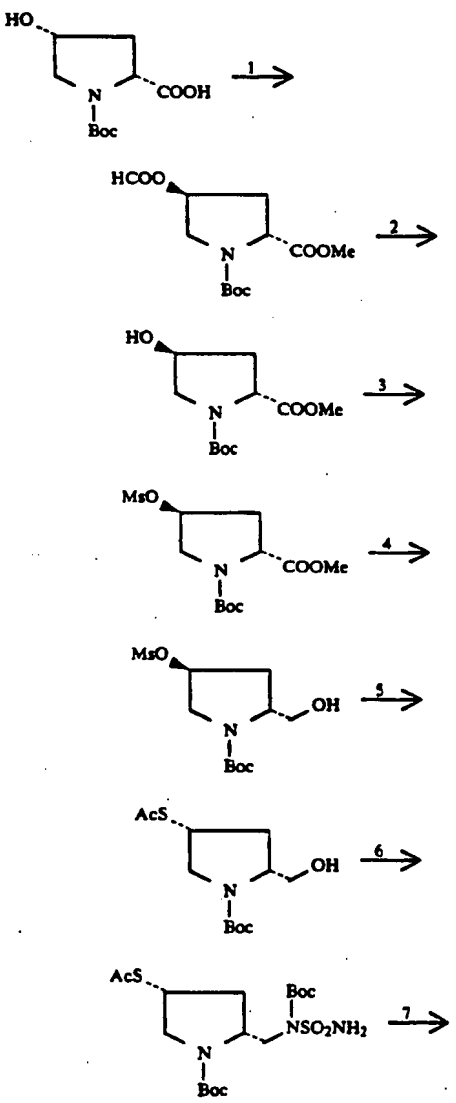
IR $\nu$ (Nujol) $cm^{-1}$: 3360, 3270, 1718, 1548. Elemental Analysis ($C_5H_{12}N_2O_4S$) Calcd.: C, 30.60; H, 6.17; N, 14.28; S, 16.34. Found: C, 30.39; H, 6.11; N, 14.30; S, 16.30.

b) Preparation of a sulfamide compound To a solution of (2R,4S)-4-acetylthio-1-t-butoxycarbonylpyrrolidine-2-methanol (i.e., a substrate) in tetrahydrofuran (THF), triphenylphosphine ($PPh_3$), N-t-butoxycarbonylsulfamide (BSMD), and azodicarboxylic acid diethyl ester (DEAD) are successively added under ice cooling. The conditions for this reaction are shown in Table 2, Step A-6. The reaction mixture is diluted with toluene, concentrated, diluted with toluene, and the formed crystals are filtered off. The filtrate is concentrated. The residue is purified by silica gel column chromatography to give (2R,4S)-4-acetylthio-1-t-butoxycarbonyl-2-(N-t-butoxycarbonyl-N-sulfamoylamino)methylpyrrolidine. NMR $\delta(CDCl_3)$ ppm: 1.41(s, 9H), 1.55(s, 9H), 1.19 to 2.0(m, 2H), 2.35(s, 3H), 3.32(dd, J=11.4 Hz, J=8.2 Hz, 1H), 3.6 to 3.9(m, 3H), 3.9 to 4.1(m, 1H), 4.5(m, 1H), 6.15(s, 2H). IR $\nu$ (KBr) $cm^{-1}$: 3420, 3320, 1706, 1686, 1666.

Step A-7. Removal of an acetyl group

To a solution of (2R,4S)-4-acetylthio-1-t-butoxycarbonyl-2-(N-t-butoxycarbonyl-N-sulfamoylamino)methylpyrrolidine (i.e., a substrate) in dichloromethane, 4.92M sodium methoxide (NaOMe) in methanol is added. The mixture is stirred. The conditions for this reaction are shown in Table 3, Step A-7. The reaction mixture is diluted with water. The water layer is taken, toluene is added thereto, and acidified with conc. hydrochloric acid under ice cooling. The organic layer is taken, successively washed with water and saturated brine, dried over magnesium sulfate, and concentrated in vacuo to give (2R,4S)-1-t-butoxycarbonyl-2-(N-t-butoxycarbonyl-N-sulfamoylamino)methyl-4-mercaptopyrrolidine. mp. 90.0° to 91.5° C. NMR $\delta(CDCl_3)$ ppm: 1.43(s, 9H), 1.52(s, 9H), 1.72(d, J=7.0 Hz, 1H), 1.9 to 2.0(m, 2H), 3.2 to 3.8(m, 5H), 4.5(m, 1H), 6.11(s, 2H). IR $\nu$ (KBr) $cm^{-1}$: 3220, 1698, 1683. Elemental Analysis ($C_{15}H_{29}O_6N_3S_2$) Calcd. C:43.78, H:7.10, N:10.21, S:15.58. Found. C:43.55, H:7.11, N:10.37, S:15.75.

PREPARATIVE EXAMPLE 7-B OF A PYRROLIDINE DERIVATIVE



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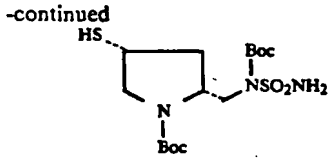


Step B-1. Substitution for a formyloxy group

To a solution of (2R,4R)-1-t-butoxycarbonyl-4-hydroxy-2-methoxycarbonylpyrrolidine (2.45 g: 10 mmole) in tetrahydrofuran (10 ml), formic acid (453 μl: 12 mmole), triphenylphosphine (3.15 g: 12 mmole), and diethyl azodicarboxylate (1.89 ml: 12 mmole) are successively is added in a nitrogen atmosphere under ice cooling. The mixture is stirred for 30 minutes at the same temperature to give (2R,4S)-1-t-butoxycarbonyl-4-formyloxy-2-methoxycarbonylpyrrolidine (2.17 g). Yield: 79%. Colorless oil. NMR δ($CDCl_3$) ppm: 1.44(d, J=7.8 Hz, 9H), 2.1 to 2.6(m, 2H), 3.5 to 3.9(m, 5H), 4.4(m, 1H), 5.4(m, 1H), 8.0(s, 1H).

Step B-2. Removal of a formyl group

To a solution of (2R,4S)-1-t-butoxycarbonyl-4-formyloxy-2-methoxycarbonylpyrrolidine (2.08 g: 7.6 mmole) in methanol (21.0 ml), aqueous 1N-sodium hydroxide (7.6 ml) is added under ice cooling. The mixture is stirred at the same temperature for 25 minutes to give (2R,4S)-1-t-butoxycarbonyl-4-hydroxy-2-methoxycarbonylpyrrolidine (1.86 g). Yield: 100%. Colorless oil. NMR δ($CDCl_3$) ppm: 1.44(d, J=9.2 Hz, 9H), 1.9 to 2.4(m, 2H), 3.4 to 3.7(m, 2H), 3.74 (s, 3H), 4.3 to 4.6(m, 2H).

Step B-3. Preparation of a mesyl compound

To a solution of (2R,4S)-1-t-butoxycarbonyl-4-hydroxy-2-methoxycarbonylpyrrolidine (3.17 g: 12.9 mmole) in dichloromethane (16 ml) in a nitrogen atmosphere under ice cooling, triethylamine (2.15 ml: 15.5 mmole) and methanesulfonyl chloride (1.19 ml: 15.5 mmole) are added. The mixture is stirred to react for 30 minutes to give (2R,4S)-1-t-butoxycarbonyl-4-methanesulfonyloxy-2-methoxycarbonylpyrrolidine as oil (4.13 g). Yield: 99%. NMR δ($CDCl_3$) ppm: 1.46(d, J=8.4 Hz, 9H), 2.3(m, 1H), 2.5 to 2.8(m, 1H), 3.08(s, 3H), 3.8 to 4.0(m, 5H), 4.3 to 4.6(m, 1H), 5.3(m, 1H).

Step B-4. Preparation of a methylol compound

To a solution of (2R,4S)-1-t-butoxycarbonyl-4-methanesulfonyloxy-2-methoxycarbonylpyrrolidine (3.96 g: 12.2 mmole) in a mixture of tetrahydrofuran (12 ml) and ethanol (18 ml), sodium borohydride (1.85 g: 48.8 mmole) is added in a nitrogen atmosphere under ice cooling. The mixture is stirred for 45 minutes at room temperature to give (2R,4S)-1-t-butoxycarbonyl-4-methanesulfonyloxypyrrolidine-2-methanol (2.97 g). Yield: 83%. Colorless crystals. mp. 95° to 96° C. NMR δ($CDCl_3$) ppm: 1.49(s, 9H), 1.7 to 2.1(m, 1H), 2.3 to 2.5(m, 1H), 3.06(s, 3H), 3.4 to 3.7(m, 2H), 3.7 to 4.0(m, 2H), 4.0 to 4.3(m, 1H), 5.2(m, 1H). IR ν (KBr) $cm^{-1}$: 3400, 3420, 1648.

Step B-5. Substitution for an acetylthio group

(2R,4S)-1-t-butoxycarbonyl-4-methanesulfonyloxypyrrolidine-2-methanol (i.e., a substrate) is allowed to react in the same manner as in Step A-5 in Preparative Example 7-A under a condition for Step B-5 shown in Table 1 to give (2R,4R)-4-acetylthio-1-t-butoxycarbonylpyrrolidine-2-methanol. NMR δ($CDCl_3$) ppm: 1.47(s, 9H), 2.34(s, 3H), 2.4 to 3.2 (m, 2H), 3.58 to 4.1(m, 6H). IR ν ($CHCl_3$) $cm^{-1}$: 3380, 1690.

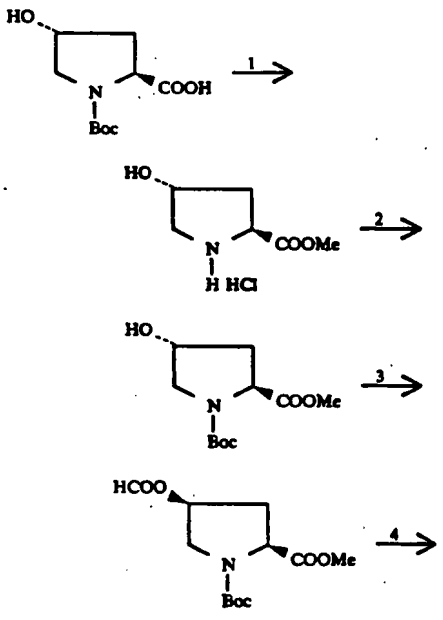
Step B-6. Introduction of a sulfamide group

N-t-butoxycarbonylsulfamide is prepared in the same manner as in the paragraph (a) of Step A-6 in Preparative Example 7-A. (2R,4R)-4-acetylthio-1-t-butoxycarbonylpyrrolidine-2-methanol (i.e., a substrate) is allowed to react with the obtained N-t-butoxycarbonylsulfamide in the similar manner as in paragraph (b) of Step A-6 in Preparative Example 7-A under a condition for Step B-6 shown in Table 2 to give (2R,4R)-4-acetylthio-1-t-butoxycarbonyl-2-(N-t-butoxycarbonyl-N-sulfamoylamino)methylpyrrolidine. NMR δ($CDCl_3$) ppm: 1.43(s, 9H), 1.53(s, 9H), 2.34(s, 3H), 2.5(m, 1H), 3.15(dd, J=12.2 Hz, J=6.2 Hz, 1H), 3.58(dd, J=14.8 Hz, J=3.2 Hz, 1H), 3.8 to 4.1(m, 2H), 4.16(dd, J=12.2 Hz, J=7.8 Hz, 1H), 4.4 to 4.7 (m, 1H), 6.11(s, 2H). IR ν ($CHCl_3$) $cm^{-1}$: 3360, 3200, 1710, 1688.

Step B-7. Removal of an acetyl group

(2R,4R)-4-acetylthio-1-t-butoxycarbonyl-2-(N-t-butoxycarbonyl-N-sulfamoylamino) methylpyrrolidine (i.e., a substrate) is deacetylated in the similar manner as in Step A-7 of Preparative Example 7-A under a condition for Step B-7 shown in Table 3 to give (2R,4R)-1-t-butoxycarbonyl-2-(N-t-butoxycarbonyl-N-sulfamoylamino)methyl-4-mercaptopyrrolidine. mp. 92° to 93° C. NMR δ($CDCl_3$) ppm: 1.2 to 1.5(m, 1H), 1.42 (s, 9H), 1.54(s, 9H), 1.82(d, J=6.2 Hz, 1H), 2.5 to 2.7(m, 1H), 4.09, 3.05 (ABX, J=12.0 Hz, J=7.4 Hz, J=8.2 Hz, 2H), 4.06, 3.62(ABX, J=15.0 Hz, J=10.8 Hz, J=3.2 Hz, 2H), 4.2 to 4.6(m, 1H), 6.08(s, 2H). IR ν ($CHCl_3$) $cm^{-1}$: 3380, 3220, 1718, 1680.

## PREPARATIVE EXAMPLE 7-C OF A PYRROLIDINE DERIVATIVE



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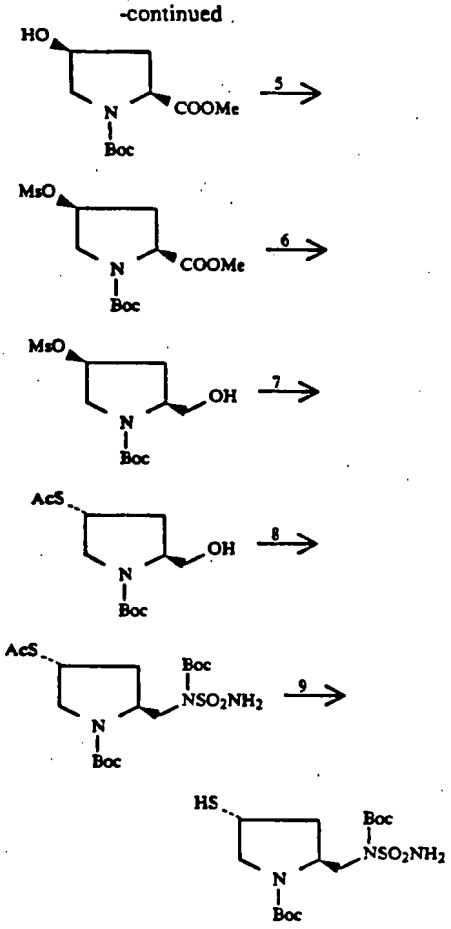



Step C-1. Preparation of an ester compound

To a suspension of trans-4-hydroxy-L-proline (200 g: 1.525 mole) in methanol (800 ml), acetylchloride (163 ml: 2.288 mole) is added dropwise under ice cooling in a nitrogen atmosphere. The mixture is warmed to room temperature, mixed with thionyl chloride (55.7 ml: 0.763 mole), and stirred for 4 hours at 40° C. to give (2S,4R)-4-hydroxy-2-methoxycarbonylpyrrolidine hydrochloride (244.27 g). Yield: 88%. Colorless crystals. NMR $\delta(D_2O)$ ppm: 1.8 to 2.0(m, 1H), 2.0 to 2.2(m, 1H), 2.9 to 3.1(m, 1H), 3.17(dd, J=12.6 Hz, J=3.6 Hz, 1H), 3.49(s, 3H), 4.2 to 4.4(m, 2H). IR $\nu$ (KBr) $cm^{-1}$: 3380, 3330, 2695, 2960, 1742.

Step C-2. Preparation of a Boc compound

To a suspension of (2S,4R)-4-hydroxy-2-methoxycarbonylpyrrolidine hydrochloride (12.71 g: 70 mmole) in dichloromethane (70 ml), triethylamine (10.7 ml: 77 mmole) is added dropwise under ice cooling in a nitrogen atmosphere. The mixture is stirred for 5 min. at room temperature. A solution of di-t-butyl dicarbonate (19.10 g: 87.5 mmole) in dichloromethane (72 ml) is added dropwise thereto, and the mixture is stirred for 45 minutes at room temperature to give (2S,4R)-1-t-butoxycarbonyl-4-hydroxy-2-methoxycarbonylpyrrolidine (14.06 g). Yield: 82%. Colorless oil. NMR $\delta(CDCl_3)$ ppm: 1.44(d, J=9.6 Hz, 9H), 1.9 to 2.4(m, 3H), 3.4 to 3.7(m, 2H), 3.74 (s, 3H), 4.3 to 4.6(m, 2H).

Step C-3. Substitution with a formyloxy group

To a solution of (2S,4R)-1-t-butoxycarbonyl-4-hydroxy-2-methoxycarbonylpyrrolidine (7.36 g: 30 mmole) in tetrahydrofuran (30 ml), formic acid (1.36 ml: 36 mmole), triphenylphosphine (9.44 g: 36 mmole) and diethyl azodicarboxylate (5.67 ml: 36 mmole) are successively added in a nitrogen atmosphere under ice cooling. The mixture is stirred to react for 40 minutes at the same temperature to give (2S,4S)-1-t-butoxycarbonyl-4-formyloxy-2-methoxycarbonylpyrrolidine (5.38 g). Yield: 66%. Colorless crystals. NMR $\delta(CDCl_3)$ ppm: 1.45(d, J=8.6 Hz, 9H), 2.2 to 2.4(m, 1H), 2.4 to 2.7(m, 1H), 3.5 to 3.9(m, 2H), 3.75(s, 3H), 4.3 to 4.6(m, 1H), 5.3 to 5.5(m, 1H), 7.98 (s, 1H). IR $\nu$ (KBr) $cm^{-1}$: 3420, 1748, 1712, 1681.

Step C-4. Removal of a formyl group

To a solution of (2S,4S)-1-t-butoxycarbonyl-4-formyloxy-2-methoxycarbonylpyrrolidine (5.12 g: 18.7 mmole) in methanol (51.0 ml), aqueous 1N-sodium hydroxide (18.7 ml) is added under ice cooling. The mixture is stirred at the same temperature for 20 minutes to give (2S,4S)-1-t-butoxycarbonyl-4-hydroxy-2-methoxycarbonylpyrrolidine (4.09 g). Yield: 89%. Colorless crystals. NMR $\delta(CDCl_3)$ ppm: 1.44(d, J=8.2 Hz, 9H), 2.0 to 2.2(m, 1H), 2.2 to 2.5(m, 1H), 3.2 to 3.8(m, 3H), 3.79(d, J=2.8 Hz, 3H), 4.2 to 4.5(m, 2H). IR $\nu$ (KBr) $cm^{-1}$: 3460, 1728, 1677.

Step C-5. Preparation of a mesyl compound

In a manner similar to Step A-3 in Preparative Example 7-A, (2S,4S)-1-t-butoxycarbonyl-4-hydroxy-2-methoxycarbonylpyrrolidine in dichloromethane is mesylated with triethylamine and methanesulfonylchloride in a nitrogen atmosphere under ice cooling to give (2S,4S)-1-t-butoxycarbonyl-4-methanesulfonyloxy-2-meth-oxycarbonylpyrrolidine. mp. 90.0° to 91.5° C.

Step C-6. Preparation of a methylol compound

In a similar manner to that in Step A-4 in Production Example 7-A, (2S,4S)-1-t-butoxycarbonyl-4-methanesulfonyloxy-2-methoxycarbonylpyrrolidine is allowed to react to give (2S,4S)-1-t-butoxycarbonyl-4-methanesulfonyloxypyrrolidine-2-methanol.

Step C-7. Preparation of an acetylthio compound

(2S,4)-1-t-butoxycarbonyl-4-methanesulfonyloxypyrrolidine-2-methanol (i.e., a substrate) is allowed to react in a similar manner to Step A-5 in Preparative Example 7-A under a condition for Step C-7 shown in Table 1 to give (2S,4R)-4-acetylthio-1-t-butoxycarbonylpyrrolidine-2-methanol. MNR $\delta(CDCl_3)$ ppm: 1.47(s, 9H), 2.05 (t, 2H), 2.34 (s, 3H), 3.0 to 3.3 (m, 1H), 3.40(dd, J=11.6 Hz, J=5.2 Hz, 1H), 3.5 to 3.9(m, 3H), 3.9 to 4.2(m, 2H).

Step C-8. Introduction of a sulfamide group

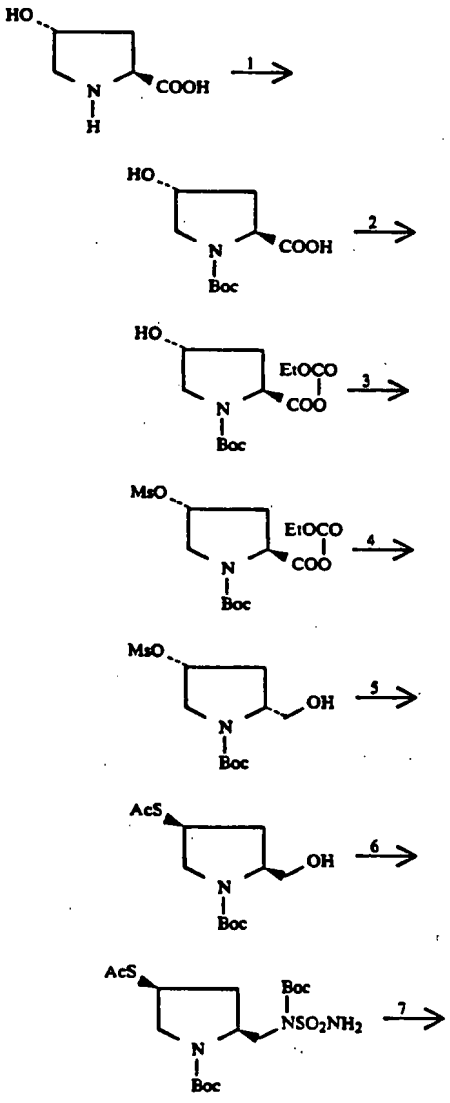
N-t-butoxycarbonylsulfamide is prepared in the same manner as in the paragraph (a) in Step A-6 in Preparative Example 7-A. (2S,4R)-4-Acetylthio-1-t-butoxycarbonylpyrrolidine-2-methanol (i.e., a substrate) is allowed to react with N-t-butoxycarbonylsulfamide in the similar manner as in the paragraph (b) in Step A-6 in Production Example 7-A under a condition for Step C-8 shown in Table 2 to give (2S,4R)-4-acetylthio-1-t-butoxycarbonyl-2-(N-t-butoxycarbonyl-N-sulfamoylamino) methylpyrrolidine. NMR $\delta(CDCl_3)$ ppm: 1.41(s, 9H), 1.55(s, 9H), 1.9 to 2.0 (m, 2H), 2.35(s, 3H),

3.32(dd, J=11.4 Hz, J=8.2 Hz, 1H), 3.6 to 3.9(m, 3H), 3.9 to 4.1(m, 1H), 4.5(m, 1H), 6.15(s, 2H). IR $\nu$ (KBr) $cm^{-1}$: 3420, 3320, 1706, 1686, 1666.

Step C-9. Removal of an acetyl group

(2S,4R)-4-acetylthio-1-t-butoxycarbonyl-2-(N-t-butoxycarbonyl-N-sulfamoylamino) methylpyrrolidine (i.e., a substrate) is allowed to react in the similar manner as in Step A-7 in Preparative Example 7-A under a condition for Step C-9 shown in Table 3 to give (2S,4R)-1-t-butoxycarbonyl-2-(N-t-butoxycarbonyl-N-sulfamoylamino) methyl-4-mercaptopyrrolidine. mp. 90.0° to 91.5° C. NMR $\delta(CDCl_3)$ ppm: 1.43(s, 9H), 1.52(s, 9H), 1.72(d, J=7.0 Hz, 1H), 1.9 to 2.0(m, 2H), 3.2 to 3.8(m, 5H), 4.5 (m, 1H), 6.11(s, 2H). IR $\nu$ (KBr) $cm^{-1}$: 3220, 1698, 1683.

## PREPARATIVE EXAMPLE 7-D OF A PYRROLIDINE DERIVATIVE

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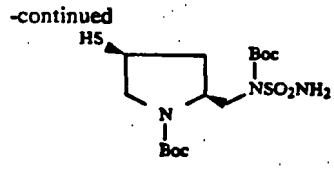



Step D-1. Preparation of an N-Boc compound

To a suspension of trans-4-hydroxy-L-proline (50 g: 0.381 mole) in methanol (250 ml), a solution of 4N-sodium hydroxide (95.4 ml: 0.381 mole) and di-t-butyl dicarbonate (91.6 g: 0.42 mole) in methanol (55 ml) is added at −20° C. The mixture is stirred at 20° C. for 3 hours. The reaction mixture is concentrated and then diluted with toluene (100 ml) and shaken. The aqueous layer is taken, and mixed with conc. hydrochloric acid (36 ml) under ice cooling, saturated brine (100 ml), and ethyl acetate (800 ml). The organic layer is taken, washed with saturated brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue is recrystallized from a toluene-ethyl acetate mixture to give (2S,4R)-1-t-butoxycarbonyl-2-carboxy-4-hydroxypyrrolidine (84.7 g). Yield: 96%. Colorless crystals. mp. 126° to 128° C. NMR $\delta(CDCl_3)$ ppm: 1.43, 1.46(2×s, 9H), 1.95 to 2.36(m, 2H), 3.36 to 3.6(m, 2H), 4.23 to 4.44(m, 2H). IR $\nu$ ($CHCl_3$) $cm^{-1}$: 3360, 1735, 1656.

Step D-2. Protection of a carboxyl group

To a solution of (2S,4R)-1-t-butoxycarbonyl-4-hydroxy-6-proline (84.5 g: 0.365 mole) in dichloromethane (1.27 liter) in a nitrogen atmosphere at −30° C., triethylamine (61.1 ml: 0.438 mole) and ethyl chloroformate (38.4 ml: 0.402 mole) are added, and the mixture is stirred for 40 minutes.

Step D-3. Preparation of an O-mesyl compound

The resulting reaction mixture containing (2S,4R)-1-t-butoxycarbonyl-2-ethoxycarbonyloxycarbonyl-4-hydroxypyrrolidine obtained in Step D-2 is cooled to −40° C., triethylamine (61.1 ml: 0.438 mole) and methanesulfonyl chloride (31.1 ml: 0.402 mole) are added thereto, and the mixture is stirred for 40 minutes.

Step D-4. Reduction

To the resulting reaction mixture containing (2S,4R)-1-butoxycarbonyl-2-ethoxycarbonyloxycarbonyl-4-methane sulfonyloxypyrrolidine obtained in Step D-3 cooling at −40° C., tetra-n-butylammonium bromide (11.8 g: 0.0365 mole) and a solution of sodium borohydride (52.5 g: 1.35 mole) in water (55 ml) are added. The mixture is allowed to warm to −10° C. and stirred for 1 hour. The aqueous layer is acidified with dilute hydrochloric acid to pH 3. The organic layer is taken, successively washed with aqueous sodium hydrogen carbonate and water, dried over magnesium sulfate, and concentrated under reduced pressure. The residue is recrystallized from a toluene-hexane mixture to give (2S,4R)-1-t-butoxycarbonyl-4-methanesulfonyloxypyrrolidine-2-methanol (101.3 g). Yield: 94%. Colorless crystals. mp. 95° to 96° C. NMR $\delta(CDCl_3)$ ppm: 1.48(s, 9H), 1.78 to 2.02(m, 1H), 2.3 to 2.48(m, 1H), 3.05 (s, 3H), 3.5 to 3.65(m, 2H), 3.65 to 4.0(m, 2H), 4.03 to 4.25 (m, 1H), 5.2(s, 1H). IR $\nu$ ($CHCl_3$) $cm^{-1}$: 3460, 1680.

Step D-5. Substitution for an acetylthio group

A solution of (2R,4S)-1-t-butoxycarbonyl-4-methanesulfonyloxypyrrolidine-2-methanol (i.e., a substrate) (11.8 g: 40 mmole) and potassium thioacetate (5.94 g: 52 mmole) in dimethylformamide (120 ml) is stirred at 65° C. for 3.75 hours. The reaction mixture is mixed with ethyl acetate (330 ml), ice water (100 ml), and 1N-hydrochloric acid (20 ml) to adjust the aqueous layer at pH 4. The organic layer is taken, successively washed with water and saturated brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel chromatography (toluene-ethyl acetate=2:1) to give (2S,4S)-4-acetylthio-1-t-butoxycarbonylpyrrolidine-2-methanol (9.48 g). Yield: 86%. Pale orange colored oil. NMR $\delta(CDCl_3)$ ppm: 1.47(s, 9H), 2.34(s, 3H), 2.4 to 3.2(m, 2H), 3.58 to 4.1(m, 6H). IR $\nu$ ($CHCl_3$) $cm^{-1}$: 3380, 1690.

Step D-6. Introduction of a sulfamide group

N-t-butoxycarbonylsulfamide is prepared in the same manner as in the paragraph (a) of Step A-6 in Preparative Example 7-A. To a solution of (2S,4S)-4-acetylthio-1-t-butoxycarbonylpyrrolidine-2-methanol (i.e., a substrate) (9.04 g: 32.8 mmole) in tetrahydrofuran (THF) (95 ml), triphenylphosphine ($PPh_3$) (10.16 g: 38.7 mmole), N-t-butoxycarbonylsulfamide (BSMD) (9.66 g: 49.2 mmole), and azodicarboxylic acid diethyl ester (DEAD) (6.20 ml: 39.4 mmole) are successively added under ice cooling. The conditions for this reaction are shown in Table 2, Step D-6. The reaction mixture is diluted with toluene (30 ml), concentrated, diluted with toluene (60 ml), and the formed crystals are filtered off. The filtrate is concentrated.

Step D-7. Removal of an acetyl group

The residue obtained in Step D-6 is dissolved in toluene (95 ml), then, 4.92M sodium methoxide in methanol (20 ml: 98.4 mmole) is added at −35° C., and the mixture is stirred for 30 minutes. The reaction mixture is diluted with water (100 ml). The aqueous layer is taken, ethyl acetate (300 ml) is added, mixed with concentrated hydrochloric acid (10 ml) under ice cooling, and the mixture is stirred. The organic layer is taken, successively washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel chromatography. Obtained colorless oil is recrystallized from toluene-hexane mixture to give (2S,4S)-1-t-butoxycarbonyl-2-(N-t-butoxycarbonyl-N-sulfamoylamino)methyl-4-mercaptopyrrolidine (9.32 g). Yield: 69%. Colorless crystals. mp. 92° to 93° C. NMR $\delta(CDCl_3)$ ppm: 1.2 to 1.5(m, 1H), 1.42(s, 9H), 1.54(s, 9H), 1.82 (d, J=6.2 Hz, 1H), 2.5 to 2.7(m, 1H), 4.09, 3.05(ABX, J=12.0 Hz, J=7.4 Hz, J=8.2 Hz, 2H), 4.06, 3.62(ABX, J=15.0 Hz, J=10.8 Hz, J=3.2 Hz, 2H), 4.2 to 4.6(m, 1H), 6.08(s, 2H). IR $\nu$ ($CHCl_3$) $cm^{-1}$: 3380, 3220, 1718, 1680. Elemental Analysis ($C_{15}H_{29}N_3O_6S_2$) Calcd.: C, 43.78; H, 7.10; N, 10.21; S, 15.58. Found: C, 43.64; H, 7.10; N, 10.19; S, 15.34.

TABLE 1

| Step | KSAc equiv.[a] | DMF vol.[b] | Temp. °C. | Time min. | Yield % |
|---|---|---|---|---|---|
| A-5 | 1.55 | 20 fold | 70 | 90 | 75 |
| B-5 | 1.20 | 5 fold | 70 | 300 | 81 |
| C-7 | 1.30 | 10 fold | 65 | 105 | 70 |

TABLE 1-continued

| Step | KSAc equiv.[a] | DMF vol.[b] | Temp. °C. | Time min. | Yield % |
|---|---|---|---|---|---|
| D-5 | 1.30 | 10 fold | 65 | 225 | 86 |

[a]Molar ratio to the substrate
[b]The volume (ml) of the solvent to the weight (g) of the substrate

TABLE 2

| Step | THF vol.[c] | $PPh_3$ equiv.[d] | BSMD equiv.[d] | DEAD equiv.[d] | Temp. | Time min. | Yield % |
|---|---|---|---|---|---|---|---|
| A-6 | 20 fold | 1.34 | 1.20 | 1.30 | 45° C. | 150 | 76 |
| B-6 | 7 fold | 1.50 | 1.66 | 1.50 | 0° C. | 300 | 84 |
| C-8 | 10 fold | 1.28 | 1.50 | 1.30 | room temp. | 240 | 82 |
| D-6 | 11 fold | 1.18 | 1.50 | 1.20 | room temp. | 180 | —[e] |

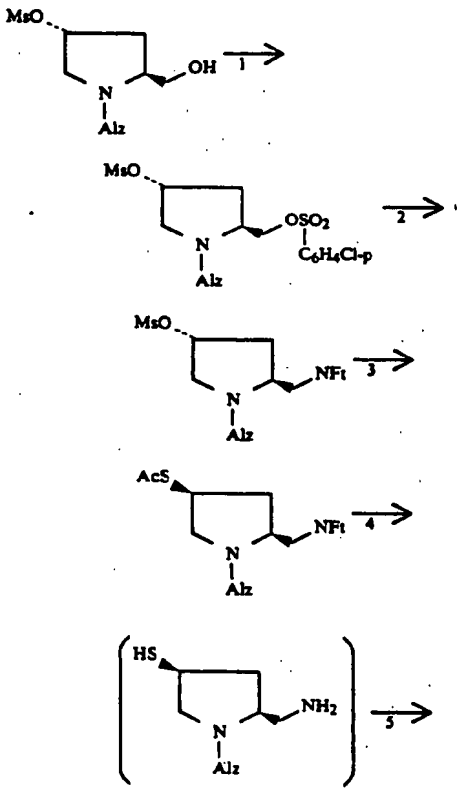
[c]The volume (ml) of the solvent to the weight (g) of the substrate
[d]Molar ratio to the substrate
[e]Not measured

TABLE 3

| Step | NaOMe equiv.[f] | Solvent[g] vol.[h] | Temp. °C. | Time min. | Yield % |
|---|---|---|---|---|---|
| A-7 | 1.5 | 15 fold | −40 | 120 | 72 |
| B-7 | 2.0 | 5 fold | −10 | 60 | 70 |
| C-9 | 3.0 | 4 fold | −35 | 30 | 85 |
| D-7 | 3.0 | 11 fold | −35 | 30 | 69 |

[f]Molar ratio to the substrate
[g]Dichloromethane is used in Steps A-7, B-7, C-9 and toluene is used in Step D-7.
[h]The volume (ml) of the solvent to the weight (g) of the substrate

PREPARATIVE EXAMPLE 8 OF A PYRROLIDINE DERIVATIVE



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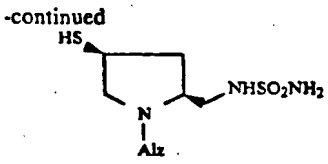


Step 1. Preparation of a p-chlorobenzenesulfonyl compound

To a solution of (2S,4R)-1-allyloxycarbonyl-4-methanesulfonyloxypyrrolidine-2-methanol (13.4 g: 50 mmole) in dichloromethane (50 ml), p-chlorobenzenesulfonyl chloride (12.66 g: 60 mmole) is added in a nitrogen atmosphere at room temperature and a solution of triethylamine (8.69 ml: 62.5 mmole) in dichloromethane (10 ml) is further added dropwise. The mixture is stirred at room temperature overnight. The reaction mixture is successively washed with aqueous sodium hydrogen carbonate and saturated brine, dried over magnesium sulfate, concentrated in vacuo, and purified by silica gel chromatography (toluene-ethyl acetate) to give crude (2S,4R)-1-allyloxycarbonyl-2-p-chlorobenzenesulfonyloxy methyl-4-methanesulfonyloxypyrrolidine (23.73 g) as oil. Yield: 105%. NMR $\delta(CDCl_3)$ ppm: 2.2 to 2.6(m, 2H), 3.04(s, 3H), 3.58(dd, J=5.0 Hz, J=11.4 Hz, 1H), 3.8 to 4.0(m, 1H), 4.1 to 4.3(m, 3H), 4.5(m, 3H), 5.1 to 5.4(m, 3H), 5.7 to 6.0(m, 1H).

Step 2. Preparation of a phthalimide compound

To a solution of (2S,4R)-1-allyloxycarbonyl-2-p-chlorobenzenesulfonyloxymethyl-4-methanesulfonyloxypyrrolidine (23.7 g: ca. 50 mmole) in dimethylformamide (50 ml), potassium phthalimide (10.2 g: 55 mmole) is added in a nitrogen atmosphere, and the mixture is stirred at 60° C. for 3.5 hours. The reaction mixture is poured into a stirring mixture of ice water (500 ml) and ethyl acetate (500 ml). The organic layer is successively washed with water (4 times) and saturated brine, dried over magnesium sulfate, and concentrated in vacuo. The residue is recrystallized from a mixture of n-hexane and toluene. The solid is filtered off and the filtrate is purified by silica gel chromatography (toluene-ethyl acetate) to give crude (2S,4R)-1-allyloxycarbonyl-2-phthalimidomethyl-4-methanesulfonyloxypyrrolidine (12.41 g). Yield: 61%. Colorless oil.

Step 3. Preparation of an acetylthio compound

A solution of (2S,4R)-1-allyloxycarbonyl-2-phthalimidomethyl-4-methanesulfonyloxypyrrolidine (12.4 g: 30.46 mmole) and 90% potassium thioacetate (5.22 g: 45.69 mmole) in dimethylformamide (130 ml) is heated with stirring at 60° C. for 4 hours. The reaction mixture is diluted with ethyl acetate (200 ml) and ice water (200 ml). The organic layer is taken, successively washed with water (3 times) and saturated brine, dried over magnesium sulfate, and concentrated in vacuo. The residue is purified by silica gel chromatography to give crude (2S,4S)-4-acetylthio-1-allyloxycarbonyl-2-phthalimidomethylpyrrolidine (9.33 g). Yield: 81%. NMR $\delta(CDCl_3)$ ppm: 1.7 to 1.9(m, 1H), 2.33(s, 3H), 2.4 to 2.7(m, 1H), 3.25 (dd, J=6.8 Hz, J=11.4 Hz, 1H), 3.7 to 4.0(m, 2H), 4.0 to 4.2(m, 2H), 4.3 to 4.6(m, 3H), 5.0 to 5.3(m, 2H), 5.7 to 5.9(m, 1H), 7.7(m, 2H), 7.85(m, 2H).

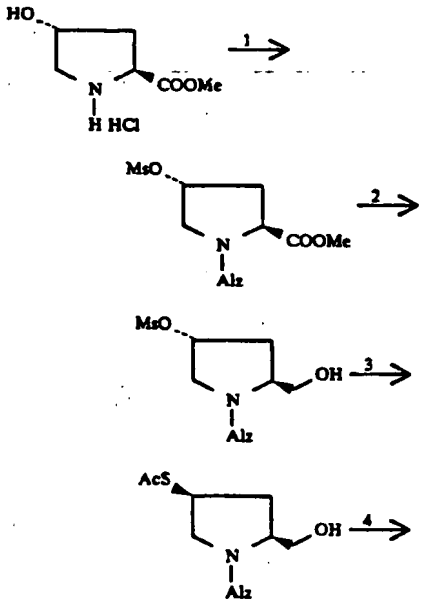
Step 4. Removal of a phthalyl and an acetyl groups

To a solution of crude (2S,4S)-1-acetylthio-1-allyloxycarbonyl-2-phthalimidomethylpyrrolidine (5.61 g: 14.90 mmole) in dichloromethane (5.4 ml), and methanol (5.4 ml), hydrazine monohydrate (2.17 ml: 44.7 mmole) is added. The mixture is heated at 60° C. with stirring for 4 hours. The solid in the reaction mixture is filtered off, washed with dichloromethane (70 ml) and the washing is combined with the filtrate. The mixture is concentrated to give crude (2S,4S)-2-aminomethyl-1-allyloxycarbonyl-4-mercaptopyrrolidine (2.80 g). Yield: 68%. Oil.

Step 5. Preparation of a sulfamoyl compound

To a solution of (2S,4S)-2-aminomethyl-1-allyloxycarbonyl-4-mercaptopyrrolidine (2.80 g: ca. 13.14 mmole) in dichloromethane (66 ml) at −50° C., triethylamine (4.02 ml: 28.91 mmole) and trimethylchlorosilane (3.76 ml: 28.91 mmole) are added dropwise over 15 minutes. The mixture is stirred at the same temperature for 20 minutes. To the reaction mixture triethylamine (0.92 ml: 6.57 mmole) and a solution of sulfamoyl chloride (19.37 mmole) in dichloromethane (6.8 ml) are added dropwise over 20 minutes at −70° C., and the mixture is stirred for 30 minutes. To the reaction mixture triethylamine (3.84 ml: 27.59 mmole) is again added over 1 hour at −50° C. The reaction mixture is kept at the same temperature overnight and concentrated in vacuo. The residual oil is purified by silica gel chromatography (ethyl acetate) to give (2S,4S)-1-allyloxycarbonyl-2-(sulfamoylamino)methyl-4-mercaptopyrrolidine (2.64 g). Yield: 68%. White powder. NMR $\delta(CDCl_3)$ ppm: 1.4 to 1.6(m, 1H), 1.83(d, J=6.2 Hz, 1H), 2.5 to 2.7(m, 1H), 3.11(dd, J=8.2 Hz, J=11.6 Hz, 1H), 3.3 to 3.4(m, 1H), 3.71(dd, J=2.9 Hz, J=15.2 Hz, 1H), 4.13(dd, J=7.3 Hz, J=11.7 Hz, 1H), 4.16(dd, J=10.3, 14.9 Hz, 1H), 4.3 to 4.6(m, 3H), 4.7(m, 2H), 5.2 to 5.4(m, 4H), 5.8 to 6.0(m, 2H), 6.0(m, 2H). IR $\nu$ $(CHCl_3)$ $cm^{-1}$: 1684, 1158.

## PREPARATIVE EXAMPLE 9 OF A PYRROLIDINE DERIVATIVE



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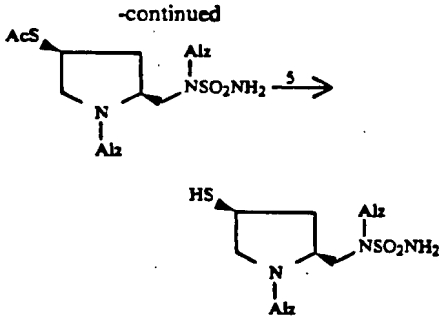


Step 1. Preparation of an N-protected and an O-mesyl compound

To a suspension of (2S,4R)-4-hydroxy-2-methoxycarbonylpyrrolidine hydrochloride (17.0 g: 100 mmole) in dichloromethane (200 ml), triethylamine (29.2 ml: 210 mmole) is added in a nitrogen atmosphere under ice cooling. The mixture is stirred for 5 minutes at room temperature, mixed dropwise with a solution of allyl chloroformate (11.2 ml: 100 mmole) in dichloromethane (20 ml), stirred for 1 hour at room temperature, and diluted with water (250 ml). The organic layer is taken, successively washed with water and saturated brine, dried over magnesium sulfate, and concentrated in vacuo to give (2S,4R)-1-allyloxycarbonyl-4-hydroxy-2-methoxycarbonylpyrrolidine (21.82 g) as oil. To a solution of this product in dichloromethane (100 ml), triethylamine (16.7 ml: 120 mmole) and methanesulfonylchloride (9.2 ml: 120 mmole) are added in a nitrogen atmosphere under ice cooling, and the mixture is stirred for 10 minutes. The reaction mixture is successively washed with aqueous sodium hydrogen carbonate and saturated brine, dried over magnesium sulfate, concentrated in vacuo, and purified by silica gel chromatography (toluene:ethyl acetate) to give (2S,4R)-1-allyloxycarbonyl-4-methanesulfonyloxy-2-methoxycarbonylpyrrolidine (27.62 g) as oil. Yield: 90%. NMR $\delta(CDCl_3)$ ppm: 2.2 to 2.4(m, 1H), 2.2 to 2.5(m, 1H), 2.5 to 2.8(m, 2H), 3.06(s, 3H), 3.74 & 3.77(2×s, 3H), 3.8 to 4.0(m, 2H), 4.4 to 4.7(m, 3H), 5.2 to 5.4(m, 3H), 5.8 to 6.0(m, 1H).

Step 2. Preparation of a methylol compound

To a solution of (2S,4R)-1-allyloxycarbonyl-4-methanesulfonyloxy-2-methoxycarbonylpyrrolidine (27.12 g: 74.0 mmole) in a mixture of tetrahydrofuran (94 ml) and ethanol (140 ml), sodium borohydride (12 g: 31.7 mmole) is added in a nitrogen atmosphere under ice cooling. The mixture is stirred for 4 hours at room temperature. To the reaction mixture concentrated sulfuric acid (8.8 ml: 158.4 mmole) is added dropwise under ice cooling. The reaction mixture is concentrated to half a volume in vacuo, and diluted with ethyl acetate (100 ml) and ice water (100 ml). The organic layer is taken, successively washed with aqueous sodium hydrogen carbonate and saturated brine, dried over magnesium sulfate, and concentrated in vacuo to give (2S,4R)-1-allyloxycarbonyl-4-methanesulfonyloxypyrrolidine-2-methanol (19.33 g). Yield: 77%. Colorless oil. NMR $\delta(CDCl_3)$ ppm: 1.9 to 2.1(m, 1H), 2.3 to 2.5(m, 1H), 3.05(s, 3H), 3.5 to 3.7(m, 2H), 3.7 to 4.1(m, 2H), 4.1 to 4.3(m, 1H), 4.6(m, 2H), 5.2 to 5.4(m, 3H), 5.8 to 6.1(m, 1H).

Step 3. Preparation of an acetylthio compound

A solution of (2S,4R)-1-allyloxycarbonyl-4-methanesulfonyloxypyrrolidine-2-methanol (19.32 g: 69.17 mmole) and 90% potassium thioacetate (10.73 g: 89.9 mmole) in dimethylformamide (217 ml) is heated with stirring at 65° C. for 5 hours. To the reaction mixture ethyl acetate (200 ml) and ice water (200 ml) are added. The organic layer is taken, successively washed with aqueous 0.05N-sodium hydroxide, 0.1N-hydrochloric acid, water and saturated brine, dried over magnesium sulfate, and concentrated in vacuo. The residue is purified by silica gel chromatography to give (2S,4S)-4-acetylthio-1-allyloxycarbonylpyrrolidine-2-methanol (15.34 g). Yield: 90%. NMR $\delta(CDCl_3)$ ppm: 1.5 to 1.7(m, 1H), 2.34(s, 3H), 2.4 to 2.6(m, 1H), 3.19(dd, J=8.0 Hz, J=11.5 Hz, 1H), 3.6 to 3.8(m, 2H), 3.8 to 4.0(m, 1H), 4.0 to 4.2(m, 2H), 4.6(m, 2H), 5.2 to 5.4(m, 2H), 5.8 to 6.1(m, 1H).

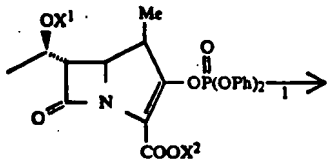
Step 4. Preparation of a sulfamide compound

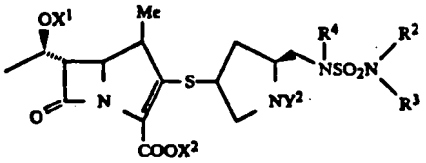
To a solution of (2S,4S)-4-acetylthio-1-allyloxycarbonylpyrrolidine-2-methanol (8.02 g: ca. 30 mmole) in ethyl acetate (83 ml) under ice cooling, triphenylphosphine (9.44 g: 13.6 mmole), N-allyloxycarbonylsulfamide (3.12 g: 15.9 mmole), and azodicarboxylic acid diethylester (5.67 ml: 36 mmole) are successively added. The mixture is stirred under ice cooling for 55 minutes and at room temperature for 4 hours. The reaction mixture is dissolved in toluene (60 ml), concentrated, diluted with toluene (60 ml), filtered to remove separating crystals, and the filtrate is concentrated. The residue is purified by silica gel chromatography to give (2S,4S)-4-acetylthio-1-allyloxycarbonyl-2-(N-sulfamoyl-N-allyloxycarbonylamino)methylpyrrolidine (6.74 g). Yield: 55%. Colorless oil. NMR $\delta(CDCl_3)$ ppm: 1.5 to 1.7(m, 1H), 2.35(s, 3H), 2.5 to 2.7(m, 1H), 3.19 (dd, J=6.3 Hz, J=11.5 Hz, 1H), 3.68(dd, J=3.8 Hz, J=14.5 Hz, 1H), 3.9 to 4.3(m, 3H), 4.3 to 4.7(m, 5H), 5.2 to 5.4(m, 4H), 5.8 to 6.1(m, 4H).

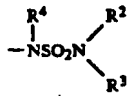
Step 5. Removal of an acetyl group

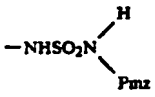
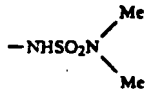
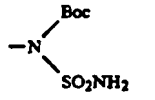
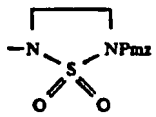
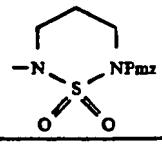
To a solution of (2S,4S)-4-acetylthio-1-allyloxycarbonyl-2-(N-sulfamoyl-N-allyloxycarbonylamino)methylpyrrolidine (6.70 g: 16.4 mmole) in toluene (50 ml), 4.92M solution of sodium methoxide in methanol (5.0 ml: 24.7 mmole) is added at −30° C. The mixture is stirred for 30 minutes, and diluted with water (55 ml). The aqueous layer is taken, diluted with toluene (50 ml), acidified with concentrated hydrochloric acid (2.3 ml) under ice cooling, and stirred. The organic layer is taken, successively washed with water and saturated brine, dried over magnesium sulfate and concentrated in vacuo. The residual oil is purified by silica gel chromatography (toluene-ethyl acetate) to give (2S,4S)-1-allyloxycarbonyl-2-(N-sulfamoyl-N-allyloxycarbonylamino)methyl-4-mercaptopyrrolidine (4.89 g). Yield: 78%. Colorless oil. NMR $\delta(CDCl_3)$ ppm: 1.5 to 1.7(m, 1H), 2.35(s, 3H), 2.5 to 2.7(m, 1H), 3.19(dd, J=6.3 Hz, J=11.5 Hz, 1H), 3.68(dd, J=3.8 Hz, J=14.5 Hz, 1H), 3.9 to 4.3(m, 3H), 4.3 to 4.7(m, 5H), 5.2 to 5.4(m, 4H), 5.8 to 6.1(m, 4H). IR $\nu(CHCl_3)$ $cm^{-1}$: 1718, 1684, 1179, 1160.

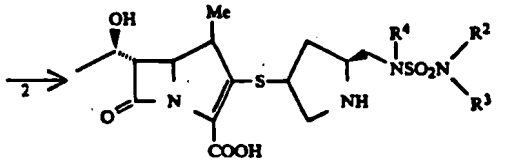
EXAMPLES

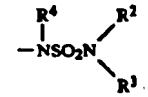


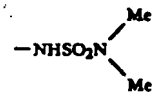
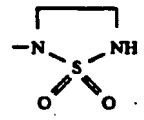
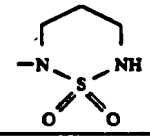




| Example | $X^1$ | $X^2$ | $Y^2$ | |
|---|---|---|---|---|
| 1 | H | PMB | Boc | $-NHSO_2NH_2$ |
| 2 | H | PNB | Pnz | $-NHSO_2NH_2$ |
| 3 | H | PMB | Pmz |  |
| 4 | H | PMB | Pmz |  |
| 5 | H | PMB | Pmz |  |
| 6 | $SiMe_3$ | $CHPh_2$ | Boc |  |
| 7 | H | PMB | Pmz | $-NHSO_2NHCH_2CH_2OH$ |
| 8 | H | PMB | Pmz |  |
| 9 | H | PMB | Pmz |  |





| Example | |
|---|---|
| 1 | $-NHSO_2NH_2$ |
| 2 | $-NHSO_2NH_2$ |
| 3 | $-NHSO_2NH_2$ |
| 4 | $-NHSO_2NHMe$ |
| 5 |  |
| 6 | $-NHSO_2NH_2$ |
| 7 | $-NHSO_2NHCH_2CH_2OH$ |
| 8 |  |
| 9 |  |

## EXAMPLE 1

Synthesis of a (3S,5S)-pyrrolidylthiocarbapenem derivative

Step 1. Preparation of a protected pyrrolidylthiocarbapenem derivative

To a solution of (1R,5S,6S)-6-[(1R)1-hydroxyethyl]-2-oxo-1-methyl-1-carbapenam-3-carboxylic acid p-methoxybenzylester (1.45 g) in acetonitrile (15 ml) at −25° C., diphenylphosphoric acid chloride (0.953 ml) and diisopropylethylamine (0.872 ml) are successively added. The mixture is stirred at room temperature for 1 hour. To this mixture 2-sulfamoylaminomethyl-1-t-butoxycarbonyl-4-mercaptopyrrolidine (1.69 g) and diisopropylethylamine (0.945 ml) are added under ice cooling, and the mixture is stirred for 22 hours. The reaction mixture is mixed with 1N-hydrochloric acid (15 ml) and diluted with ethyl acetate. The organic layer is taken, washed with water, dried over sodium sulfate and concentrated. The residue is purified by column chromatography over 10% wet silica gel to give (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(3S,5S)-5-sulfamoylaminomethyl-1-t-butoxycarbonylpyrrolidine-3-yl]thio-1-methyl-1-carba-2-penem-3-carboxylic acid p-methoxybenzylester (1.61 g). Yield: 60%. Pale yellow foam. NMR δ($CDCl_3$) ppm: 1.25(d, J=7.2 Hz, 3H), 1.32(d, J=6.4 Hz, 3H), 1.47(s, 9H), 1.75 to 2.0(m, 1H), 2.4 to 2.65(m, 1H), 2.61(br s, 4H), 3.1 to 3.7 (m, 6H), 3.81(s, 3H), 3.75 to 4.25(m, 4H), 5.19, 5.25(ABq, J=12.1

Hz, 2H), 6.89(d, J=8.6 Hz, 2H), 7.39(d, J=8.6 Hz, 2H). IR ν ($CHCl_3$) $cm^{-1}$: 3400, 3290, 1770, 1682.

Step 2. Deprotection

To a solution of (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(3S,5S)-5-sulfamoylaminomethyl-1-t-butoxycarbonylpyrrolidin-3-yl]thio-1-methyl-1-carba-2-penem-3-carboxylic acid p-methoxybenzylester (1.083 g) in a mixture of dichloromethane (16.5 ml), anisole (1.52 ml) and nitromethane (3.1 ml) at −60° C., a solution of 1.0M aluminum chloride in nitromethane (12.93 ml) is added dropwise. The mixture is stirred for 2 hours slowly warming up to −40° C. The reaction mixture is poured into a solution of sodium acetate (3.18 g) in water (24 ml), successively washed with ether and ether-petroleum ether, desalted and purified by styrene-divinylbenzene copolymer resin column chromatography, and lyophilized the objective fraction to give (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(3S,5S)-5-sulfamoylaminomethyl-1-pyrrolidin-3-yl]thio-1-methyl-1-carba-2-penem-3-carboxylic acid (0.429 g). Yield: 67%. Pale yellow foam. NMR δ($D_2O$) ppm: 1.22(d, J=7.2 Hz, 3H), 1.27(d, J=6.3 Hz, 3H), 1.64 to 1.82(m, 1H), 2.62 to 2.80(m, 1H), 3.26 to 3.59(m, 5H), 3.63 to 3.76(m, 1H), 3.84 to 4.10 (m, 2H), 4.16 to 4.29(m, 2H). IR ν (KBr) $cm^{-1}$: 3400, 1750. MIC (γ/ml): *Staphylococcus aureus* strain 3626: 25, *Streptococcus pyogenes* C203:<0.003.

## EXAMPLE 2

Coupling 2 of a (3S,5S)-pyrrolidylthiocarbapenem derivative

Step 1. Preparation of a Protected pyrrolidylthiocarbapenem derivative

To a solution of (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-diphenoxyphosphonyloxy-1-methyl-1-carba-2-penem-3-carboxylic acid p-nitrobenzylester (3.04 g: 5.12 mmole) in acetonitrile (30 ml) under ice cooling, a solution of diisopropylethylamine (1.16 ml: 1.3 eq.) and 2-sulfamoylaminometyl-1-p-nitrobenzyloxycarbonyl-4-mercaptopyrrolidine (2.4 g: 1.2 eq.) in acetonitrile (20 ml) is added. The mixture is stirred under ice cooling for 140 minutes. The reaction mixture is diluted with ethyl acetate, successively washed with water and saturated brine, dried over magnesium sulfate and concentrated. The residue is purified by silica gel column chromatography (toluene:ethyl acetate) to give (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(3S,5S)-5-sulfamoylaminomethyl-1-p-nitrobenzyloxycarbonylpyrrolidin-3-yl]thio-1-methyl-1-carba-2-penem-3-carboxylic acid p-nitrobenzylester (3.35 g). Yield: 89%. NMR δ($CDCl_3$) ppm: 1.28(d, J=7 Hz, 3H), 1.37(d, J=6 Hz, 3H), 4.68(s, 2H), 5.22, 5.50(ABq, J=14 Hz, 2H), 5.23(s, 2H), 7.52(d, J=9 Hz, 2H), 7.65 (d, J=9 Hz, 2H), 8.21(d, J=2.5 Hz, 2H), 8.26(d, J=2.5 Hz, 2H). IR ν ($CHCl_3$) $cm^{-1}$: 1773, 1720, 1704.

Step 2. Deprotection

To a solution of (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(3S,5S)-5-sulfamoylaminomethyl-1-p-nitrobenzyloxycarbonylpyrrolidin-3-yl]thio-1-methyl-1-carba-2-penem-3-carboxylic acid p-nitrobenzylester (3 g) in a mixture of tetrahydrofuran (60 ml) and 0.1 M-MES buffer (pH 7.0), 10% palladium on carbon (2 g) as a catalyst is added. The mixture is shaken under a stream of hydrogen at atmospheric pressure for 4 hours. The reaction mixture is filtered to remove the catalyst, washed with ethyl acetate to remove a neutral substance, and concentrated. The residual aqueous solution is purified by styrene-divinylbenzene copolymer resin column chromatography. The fraction eluting with 5 to 10% ethanol water is lyophilized to give (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(3S,5S)-5-sulfamoylaminomethyl-1-pyrrolidin-3-yl]thio-1-methyl-1-carba-2-penem-3-carboxylic acid (1.42 g). Yield: 84.8%.

## EXAMPLE 3

Synthesis of a (3S,5S)-pyrrolidylthiocarbapenem derivative

Step 1. Preparation of a protected pyrrolidylthiocarbapenem derivative

To a solution of (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-diphenoxyphosphonyloxy-1-methyl-1-carba-2-penem-3-carboxylic acid p-methoxybenzylester (1 mmole) in acetonitrile (10 ml) under ice cooling, diisopropylethylamine (1.2 mmole) and 2-p-methoxybenzyloxycarbonylsulfamoylaminomethyl-1-p-methoxybenzyloxycarbonyl-4-mercaptopyrrolidine (1 mmole) are added. The mixture is allowed to stand overnight. The reaction mixture is diluted with dichloromethane, successively washed with dilute hydrochloric acid, water, aqueous sodium hydrogen carbonate, and brine, dried and concentrated. The residue is purified by silica gel column chromatography to give (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(3S,5S)-5-p-methoxybenzyloxycarbonylsulfamoylaminomethyl-1-p-methoxybenzyloxy-carbonylpyrrolidin-3-yl]thio-1-methyl-1-carba-2-penem-3-carboxylic acid p-methoxybenzylester. Yield: 50 to 80%. NMR δ($CDCl_3$) ppm: 1.20(d, J=6.4 Hz, 3H), 1.34(d, J=6.1 Hz, 3H), 3.79(s,9H), 5.00 to 5.12(m, 4H), 5.23, 5.15(ABq, J=14.0 Hz, 2H). IR ν ($CHCl_3$) $cm^{-1}$: 3390, 1770, 1740, 1693, 1610.

Step 2. Deprotection

To a solution of (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(3S,5S)-5-p-methoxybenzyloxycarbonylsulfamoylaminomethyl-1-p-methoxybenzyloxycarbonylpyrrolidin-3-yl]thio-1-methyl-1-carba-2-penem-3-carboxylic acid p-methoxybenzylester (1 mmole) in dichloromethane (20 ml) at −40° C., anisole (10 mmole) and a solution of 2M aluminum chloride in nitromethane (3 to 4 ml) are added. The mixture is stirred at the same temperature for 1 to 1.5 hours. The reaction mixture is poured into a solution of sodium acetate (19 to 25 mmole) in water (100 ml), washed with dichloromethane to remove a neutral substance. The aqueous layer is purified by styrene-divinylbenzene copolymer resin column chromatography. The objective eluate is lyophlized to give (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(3S,5S)-5-sulfamoylaminomethyl-1-pyrrolidin-3-yl]thio-1-methyl-1-carba-2-penem-3-carboxylic acid. Yield: 60 to 70%.

## EXAMPLE 4

Synthesis of a (3S,5S)-pyrrolidylthiocarbapenem derivative

Step 1. Preparation of a protected pyrrolidylthiocarbapenem derivative

To a solution of (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-diphenoxyphosphonyloxy-1-methyl-1-carba-2-penem-3-carboxylic acid p-methoxybenzylester (700 mg) in acetonitrile (4 ml) at −30° C., a solution of diisopropylethylamine (182 μl) and 1-p-methoxybenzyloxy-

ycarbonyl-4-mercapto-2-(N-p-methoxybenzyloxycarbonyl-N-methylaminosulfonylaminomethyl)pyrrolidine (401 mg) in acetonitrile (3 ml) is added. The mixture is stirred under ice cooling for 90 minutes. The reaction mixture is poured into a mixture of ethyl acetate and dilute hydrochloric acid. The ethyl acetate layer is taken, successively washed with water, aqueous sodium hydrogen carbonate, and brine, dried over magnesium sulfate, and concentrated in vacuo. The residue is purified by silica gel column chromatography (toluene:ethyl acetate=1:2) to give (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(3S,5S)-1-p-meth-oxybenzyloxycarbonyl-5-(N-p-methoxybenzylcarbonyl-nyl-N-methylaminosulfonylaminomethyl)pyrrolidin-3-yl]thio-1-methyl-1-carba-2-penem-3-carboxylic acid p-methoxybenzylester (512 mg). NMR δ($CDCl_3$) ppm: 1.22(d, J=7.0 Hz, 3H), 1.34(d, J=6.4 Hz, 3H), 1.6 to 1.9(m, 1H), 2.25 to 2.5(m, 1H), 3 to 3.6(m, 7H), 3.778(s, 3H), 3.783(s, 3H), 3.788(s, 3H), 5.05(s, 2H), 5.13(s, 2H), 5.2(ABq, J=12 Hz, 2H), 6.3 to 6.5(m, 1H), 6.8 to 7.0(m, 6H), 7.2 to 7.4(m, 6H). IR ν ($CHCl_3$) $cm^{-1}$: 1767, 1697.

Step 2. Deprotection

To a solution of (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(3S,5S)-1-p-methoxybenzyloxycarbonyl-5-(N-p-methoxybenzyloxycarbonyl-N-methylaminosulfonylaminomethyl)pyrrolidin-3-yl]thio-1-methyl-1-carba-2-penem-3-carboxylic acid p-methoxybenzylester (610 mg) in a mixture of dichloromethane (6 ml), nitromethane (2 ml) and anisole (4 ml) stirring at −40° C., 2M-solution of aluminum chloride in nitromethane (2.6 ml: 7.5 equivalents) is added. The mixture is stirred at −35°±5° C. for 1 hour and 30 minutes. The reaction mixture is poured into a mixture of sodium acetate(1.34 g), water (20 ml) and dichloromethane (20 ml). The aqueous layer is taken, subjected to a styrene-divinylbenzene copolymer resin column chromatography, and the fraction eluting with 8% ethanol is lyophilized to give (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(3S,5S)-5-N-methylaminosulfonylamino-methylpyrrolidin-3-yl]thio-1-methyl-1-carba-2-penem-3-carboxylic acid (206 mg). Yield: 68.6%. NMR δ($CDCl_3$) ppm: 1.22(d, J=7.0 Hz, 3H), 1.27(d, J=6.4 Hz, 3H), 1.5 to 1.8(m, 1H), 2.63(s, 3H), 2.6 to 2.8(m, 1H), 3.1 to 3.6(m, 5H), 3.65, 3.72(dd, J=6.6 Hz, J=7.6 Hz, 1H), 3.8 to 4.4(m, 4H). IR ν ($CHCl_3$) $cm^{-1}$: 1750, 1585. MIC (γ/ml): *Staphylococcus aureus* strain 3626: 25, *Streptococcus pyogenes* C203: <0.003.

## EXAMPLE 5

Synthesis of a (3S,5S)-pyrrolidylthiocarbapenem derivative

Step 1. Preparation of a protected pyrrolidylthiocarbapenem derivative

To a solution of (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-diphenoxyphosphonyloxy-1-methyl-1-carba-2-penem-3-carboxylic acid p-methoxybenzylester (1 mmole) in acetonitrile (10 ml) under ice cooling, di-isopropylethylamine (1.2 mmole) and 2-N,N-dimethylsulfamoylaminomethyl-1-p-methoxybenzyloxycarbonyl-4-mercaptopyrrolidine (1 mmole) are added. The mixture is allowed to stand overnight. The reaction mixture is diluted with dichloromethane, successively washed with dilute hydrochloric acid and water, dried, and concentrated. The residue is purified by silica gel column chromatography to give (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(3S,5S)-5-N,N-dimethylsulfamoylaminomethyl-1-p-methoxybenzyloxycarbonylpyrrolidin-3-yl]thio-1-methyl-1-carba-2-penem-3-carboxylic acid p-methoxybenzylester. Yield: 50 to 80%. NMR δ($CDCl_3$) ppm: 1.22(d, J=7.2 Hz, 3H), 1.34(d, J=6.2 Hz, 3H), 2.76(S, 6H), 3.79(s, 3H), 3.81(s, 3H), 5.06(s, 2H), 5.24, 5.18(ABq, J=12 Hz, 2H). IR ν ($CHCl_3$) $cm^{-1}$: 3390, 1770, 1725, 1690, 1610.

Step 2. Deprotection

A solution of (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(3S,5S)-5-N,N-dimethylsulfamoylaminomethyl-1-p-methoxybenzyloxycarbonylpyrrolidin-3-yl]thio-1-methyl-1-carba-2-penem-3-carboxylic acid p-methoxybenzylester (1 mmole) in dichloromethane (20 ml) is cooled to −40° C. Anisole (10 mmole) and a solution of 2M aluminum chloride in nitromethane (3 to 4 ml) are added thereto, and the mixture is stirred at the same temperature for 1 to 1.5 hours. The reaction mixture is poured into a solution of sodium acetate (19 to 25 mmole) in water (100 ml), and washed with dichloromethane to remove a neutral material. The aqueous layer is purified by styrene-divinylbenzene copolymer resin column chromatography and the objective eluate is lyophilized to give (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(3S,5S)-5-N,N-dimethylsulfamoylaminomethylpyrrolidin-3-yl]thio-1-methyl-1-carba-2-penem-3-carboxylic acid. Yield: 60 to 70%. NMR δ($D_2O$) ppm: 1.2(d, J=7.4 Hz, 3H), 1.28(d, J=6.4 Hz, 3H), 1.65 to 1.80(m, 1H), 2.65 to 2.80(m, 1H), 2.81(s, 6H), 3.29 to 3.55(m, 5H), 3.65 to 3.75(m, 1H), 3.80 to 4.10(m, 2H), 4.16 to 4.30(m, 2H). IR ν (KBr) $cm^{-1}$: 3400, 1750. MIC (γ/ml): *Staphylococcus aureus* strain 3626: 25, *Streptococcus pyogenes* C203: <0.003.

## EXAMPLE 6

Synthesis of a (3S,5S)-pyrrolidylthiocarbapenem derivative

Step 1. Preparation of a protected pyrrolidylthiocarbapenem derivative

To a solution of (1R,5S,6S)-2-diphenoxyphosphonyloxy-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid diphenylmethylester (6.88 g: 11 mmole) in dichloromethane (70 ml) under ice cooling, trimethylchlorosilane (1.81 ml: 14.3 mmole) and triethylamine (1.99 ml: 14.3 mmole) are added. The mixture is stirred for 25 minutes. The reaction mixture is poured into aqueous sodium hydrogen carbonate. The organic layer is taken, washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue containing the product, (1R,5S,6S)-2-diphenoxyphosphonyloxy-1-methyl-6-[(1R)-1-trimethylsilyloxyethyl]-1-carba-2-penem-3-carboxylic acid diphenylmethylester is dissolved in acetonitrile (70 ml), and (2S,4S)-1-t-butoxycarbonyl-2-(N-t-butoxycarbonyl-N-sulfamoylamino)methyl-4-mercaptopyrrolidine (5.43 g: 13.2 mmole) and diisopropylethylamine (2.30 g: 13.2 mmole) are added thereto under ice cooling. The obtained mixture is stirred for 4.5 hours. To the reaction mixture containing the product, (1R,5S,6S)-2-[(3S,5S)-1-t-butoxycarbonyl-5-(N-t-butoxycarbonyl-N-sulfamoylamino)methylpyrrolidin-3-yl]thio-1-methyl-6-[(1R)-1-trimethylsilyloxyethyl]-1-carba-2-penem-3-carboxylic acid diphenylmethylester, 1N-hydrochloric acid (5.5 ml) is added, and the mixture is stirred for 20 minutes, diluted with ethyl acetate(150 ml), and the mixture is poured into ice water. The organic layer is taken, successively washed with aqueous

sodium hydrogen carbonate, water, and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue is recrystallized from toluene to give (1R,5S,6S)-2-[(3S,5S)-1-t-butoxycarbonyl-5-(N-t-butoxycarbonyl-N-sulfamoylamino)methylpyrrolidin-3-yl]thio-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid diphenylmethylester (7.53 g). Yield: 87%. Colorless crystals. mp.163° to 164° C. NMR $\delta(CDCl_3)$ ppm: 1.27(d, J=7.2 Hz, 3H), 1.39(s, 9H), 1.42(s, 9H), 2.45 to 2.65(m, 1H), 3.1 to 3.35(m, 2H), 3.28(dd, J=7.2 Hz, J=2.6 Hz, 1H),3.5 to 3.77(m, 2H), 3.9 to 4.15(m, 2H), 4.26(dd, J=7.0 Hz, J=2.6 Hz, 1H), 4.2 to 4.37(m, 1H), 4.45 to 4.66(m, 1H), 6.07(s, 2H), 6.95(s, 1H), 7.2 to 7.6(m, 10H). IR $\nu$ ($CHCl_3$) $cm^{-1}$: 3385, 3230, 1778, 1715, 1685.

Elemental Analysis ($C_{38}H_{50}N_4O_{10}S_2$) Calcd.; C, 57.99; H, 6.40; N, 7.12; S, 8.15. Found: C, 57.87; H, 6.46; N, 6.99; S, 7.93.

Step 2. Deprotection

To a solution of aluminum chloride (3.20 g: 24 mmole) in a mixture of anisole (24 ml) and dichloromethane (24 ml) at −40° C., a solution of (1R,5S,6S)-2-[(3S,5S)-1-t-butoxycarbonyl-5-(N-t-butoxycarbonyl-N-sulfamoyl-amino)methylpyrrolidin-3-yl]thio-6-[(1R)-1-hydroxy-ethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid diphenylmethylester (2.36 g: 3 mmole) in dichloromethane (12 ml) is dropwise and gradually added. The mixture is vigorously stirred at −25° to −30° C. for 3.5 hours. The reaction mixture is poured into a solution of sodium acetate (5.91 g: 72 mmole) in water (48 ml). The aqueous layer is taken, washed with dichloromethane, concentrated in vacuo to remove remaining orgaic solvent and subjected to styrene-divinylbenzene copolymer resin column chromatography. The fraction eluting with methanol-water (1:9) is lyophilized to give (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(3S,5S)-5-sulfamidomethylpyrrolidin-3-yl]thio-1-methyl-1-carba-2-penem-3-carboxylic acid (910 mg). Yield: 72%. Colorless foam. NMR $\delta(D_2O)$ ppm: 1.22(d, J=7.2 Hz, 3H), 1.27(d, J=6.3 Hz, 3H), 1.64 to 1.82(m, 1H), 2.62 to 2.80(m, 1H), 3.26 to 3.59(m, 5H), 3.63 to 3.76(m, 1H), 3.84 to 4.10(m, 2H), 4.16 to 4.29(m, 2H). IR $\nu$ (KBr) $cm^{-1}$: 3400, 1750. MIC ($\gamma$/ml): *Staphylococcus aureus* 3626: 25. Blood level: mice i.v., after 15 min. ($\gamma$/ml): 9.8. Urinary recovery: mice i.v., (%): 36.3.

## EXAMPLE 7

Synthesis of a (3S,5S)-pyrrolidylthiocarbapenem derivative

Step 1. Preparation of a protected pyrrolidylthiocarbapenem derivative

To a solution of (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-oxo-1-carbapenam-3-carboxylic acid p-methoxybenzylester (277 mg) in acetonitrile (4 ml) under ice cooling, diphenylphosphoric acid chloride (198 µl) and diisopropylethylamine (166 µl) are successively added. The mixture is stirred at room temperature for 1 hour. To the reaction mixture containing the product, (1R,5S,6S)-2-diphenoxyphosphonyloxy-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid p-methoxybenzylester, (2S,4S)-2-(2)-hydroxyethyl)sulfamoylaminomethyl-1-p-methoxybenzyloxy-carbonyl-4-mercaptopyrrolidine (344 mg) and diisopropylethylamine (166 µl) are added under ice cooling, and the mixture is stirred at the same temperature for 2 hours. The reaction mixture is diluted with ethyl acetate, successively washed with water, dilute hydrochloric acid, water, aqueous sodium hydrogen carbonate and water, dried over magnesium sulfate, and concentrated. The residue is purified by silica gel column chromatography to give (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(3S,5S)-5-(2-hydroxyethyl)sulfamoylaminomethyl-1-p-methoxybenzyloxycarbonyl-pyrrolidin-3-yl]thio-1-methyl-1-carba-2-penem-3-carboxylic acid p-methoxybenzylester (156 mg). Yield: 26%. NMR $\delta(CDCl_3)$ ppm: 1.22(d, J=7.0 Hz, 3H), 1.34(d, J=6.2 Hz, 3H), 3.79(s, 3H), 3.80(s, 3H), 5.05(s, 2H), 5.17, 5.24(ABq, J=12.2 Hz, 2H). IR $\nu$ ($CHCl_3$) $cm^{-1}$: 1775, 1690.

Step 2. Deprotection

To a solution of (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(3S,5S)-5-(2-hydroxyethyl)sulfamoylaminomethyl-1-p-methoxybenzyloxycarbonylpyrrolidin-3-yl]thio-1-methyl-1-carba-2-penem-3-carboxylic acid p-methoxybenzyl ester (148 mg) in a mixture of dichloromethane (3 ml) and nitromethane (750 µl) in a nitrogen atmosphere at −40° C., a solution of 1.0M aluminum chloride in nitromethane (1.8 ml) and anisole (258 µl) is added. The mixture is stirred at the same temperature for 1.5 hours. The reaction mixture is poured into a solution of sodium acetate (454 mg) in water (8 ml) and washed with an ether-hexane mixture. The aqueous layer is concentrated in vacuo to 4 ml, and purified by styrene-divinylbenzene copolymer resin column chromatography to give (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(3S,5S)-5-(2-hydroxyethyl)sulfamoylaminomethylpyrrolidin-3-yl]thio-1-methyl-1-carba-2-penem-3-carboxylic acid (42 mg). Yield: 46%. NMR $\delta(D_2O)$ ppm: 1.21(d, J=7.4 Hz, 3H), 1.28(d, J=6.4 Hz, 3H), 1.66 to 1.81(m, 1H), 2.66 to 2.81(m, 1H), 3.15(t, J=5.6 Hz, 2H), 3.32 to 3.54(m, 5H), 3.65 to 3.75(m, 3H), 3.87 to 4.07(m, 2H), 4.18 to 4.27(m, 2H). IR $\nu$ (KBr) $cm^{-1}$: 3400, 1750. Blood level: mice i.v., after 15 min ($\gamma$/ml): 29.3.

## EXAMPLE 8

Synthesis of a (3S,5S)-pyrrolidylthiocarbapenem derivative

Step 1. Preparation of a protected pyrrolidylthiocarbapenem derivative

To a solution of (1R,5S,6S)-2-diphenoxyphosphonyloxy-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid p-methoxybenzylester (456 mg) in acetonitrile (3 ml) under ice cooling, diisopropylethylamine (165 µl) and (2S,4S)-2-(1,1-dioxo-2-p-methoxybenzyloxycarbonyl-1,2,5-thiadiazolidin-5-yl)methyl-4-mercapto-1-p-methoxybenzyloxycarbonyl-pyrrolidine (445 mg) are added. The mixture is allowed to stand at 0° C. overnight. The reaction mixture is diluted with ethyl acetate, successively washed with water, dilute hydrochloric acid and water, dried over magnesium sulfate, and concentrated in vacuo. The residue is purified by silica gel chromatography to give (1R,5S,6S)-2-[(3S,5S)-5-(1,1-dioxo-2-p-methoxybenzyloxycarbonyl-1,2,5-thiadiazolidin-5-yl)methyl-1-p-methoxybenzyloxycarbonylpyrrolidin-3-yl]thio-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid p-methoxybenzylester (510 mg). Yield: 72%. NMR $\delta(CDCl_3)$ ppm: 1.22(d, J=7.4 Hz, 3H), 1.34(d, J=6.2 Hz, 3H), 5.04(s, 2H), 5.23(s, 2H), 5.18,

5.24(ABq, J=11.9 Hz, 2H). IR ν ($CHCl_3$) $cm^{-1}$: 1773, 1735, 1700.

Step 2 Deprotection

To a solution of (1R,5S,6S)-2-[(3S,5S)-5-(1,1-dioxo-2-p-methoxybenzyloxycarbonyl-1,2,5-thiadi-azolidin-5-yl)methyl-1-p-methoxybenzyloxycarbonylpyrrolidin-3-yl]thio-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid p-methoxybenzylester (500 mg) in a mixture of dichloromethane (8 ml) and nitromethane (3 ml) in a nitrogen atmosphere at −40° C., anisole (729 μl) and a solution (5.03 ml) of 1.0M aluminum chloride in nitromethane are added. The mixture is stirred at the same temperature for 1.5 hours. The reaction mixture is poured into a solution of sodium acetate (1.28 g) in water (50 ml), then aqueous layer is taken, and washed with an ether-hexane mixture. The aqueous layer is concentrated under reduced pressure to about 15 ml, and is purified by styrene-divinylbenzene copolymer resin column chromatography to give (1R,5S,6S)-2-[(3S,5S)-5-(1,1-dioxo-1,2,5-thiadiazolidin-5-yl)methylpyrrolidin-3-yl]thio-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid (180 mg). Yield: 72%. NMR δ($D_2O$) ppm: 1.21(d, J=7.4 Hz, 3H), 1.28(d, J=6.4 Hz, 3H), 1.68 to 1.84(m, 1H), 2.71 to 2.85(m, 1H), 3.28 to 3.77(m, 10H), 3.94 to 4.12(m, 2H), 4.17 to 4.31(m, 2H).

IR ν (KBr) $cm^{-1}$: 3400, 1750.

MIC (γ/ml): *Staphylococcus aureus* strain 3626: 25.

Blood level: mice i.v., after 15 min (γ/ml): 31.8.

## EXAMPLE 9

Synthesis of a (3S,5S)-pyrrolidylthiocarbapenem derivative

Step 1. Preparation of a protected pyrrolidylthiocarbapenem derivative

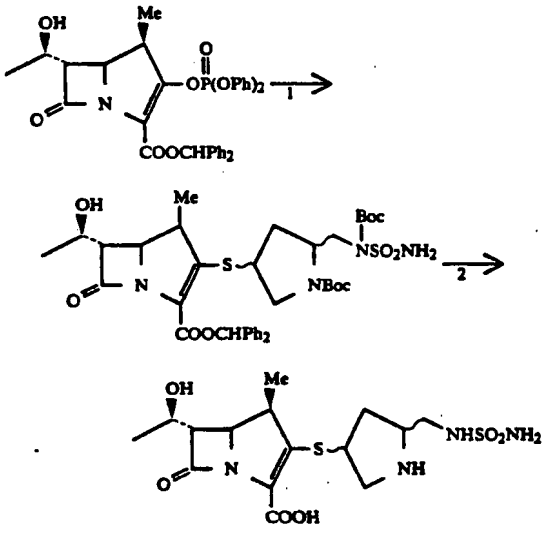
To a solution of (1R,5S,6S)-2-diphenoxyphosphonyloxy-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid p-methoxybenzyl ester (638 mg) in acetonitrile (6 ml) under ice cooling, diisopropylethylamine (230 μl) and (2S,4S)-2-(1,1-dioxo-2-p-methoxybenzyloxycarbonyl-3,4,5,6-tetrahydro-1,2,6-thiadiazin-6-yl)methyl-4-mercapto-1-p-methoxybenzyloxycarbonylpyrrolidine (700 mg) are added. The mixture is stirred at 5° C. for 2 hours and at room temperature for 1 hour. The reaction mixture is diluted with ethyl acetate, successively washed with water, dilute hydrochloric acid, water, aqueous sodium hydrogen carbonate and water, dried over magnesium sulfate, and concentrated in vacuo. The residue is purified by silica gel chromatography to give (1R,5S,6S)-2-[(3S,5S)-5-(1,1-dioxo-2-p-methoxybenzyloxycarbonyl-3,4,5,6-tetrahydro-1,2,6-thiadiazin-6-yl)methyl-1-p-methoxybenzyloxycarbonylpyrrolidin-3-yl]thio-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid p-methoxybenzyl ester (640 mg). Yield: 65%. NMR δ($CDCl_3$) ppm: 1.22(d, J=7.4 Hz, 3H), 1.34(d, J=6.4 Hz, 3H), 5.04(s, 2H), 5.17, 5.25(ABq, J=12.3 Hz, 2H), 5.19(s, 2H). IR ν ($CHCl_3$) $cm^{-1}$: 1700, 1770.

Step 2. Deprotection

To a solution of (1R,5S,6S)-2-[(3S,5S)-5-(1,1-dioxo-2-p-methoxybenzyloxycarbonyl-3,4,5,6-tetrahydro-1,2,6-thiadiazin-6-yl)methyl-1-p-methoxybenzyloxycarbonylpyrrolidin-3-yl]thio-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid p-methoxybenzylester (600 mg) in a mixture of dichloromethane (9 ml) and nitromethane (3.5 ml) in a nitrogen atmosphere at −40° C., anisole (861 μl) and a solution of 1.0M aluminum chloride in nitromethane (5.94 ml) are added. The mixture is stirred at the same temperature for 1.5 hours. The reaction mixture is poured into a solution of sodium acetate (1.52 g) in water (50 ml), and washed with a mixture of ether and hexane. The aqueous layer is concentrated in vacuo to about 15 ml, and the mixture is purified by styrene-divinylbenzene copolymer resin column chromatography to give (1R,5S,6S)-2-[(3S,5S)-5-(1,1-dioxo-3,4,5,6-tetrahydro-1,2,6-thiadiazin-6-yl)methylpyrrolidin-3-yl]thio-6-[(1R)-1-hydroxy-ethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid (190 mg). Yield: 63%. NMR δ($D_2O$) ppm: 1.20(d, J=7.2 Hz, 3H), 1.27(d, J=6.4 Hz, 3H), 1.65 to 1.80(m, 3H), 2.65 to 2.80(m, 1H), 3.27 to 3.56(m, 9H), 3.64 to 3.74(m, 1H), 3.91 to 4.10(m, 2H), 4.15 to 4.30(m, 2H). IR ν (KBr) $cm^{-1}$: 3400, 1750. MIC (γ/ml): *Staphylococcus aureus* strain 3626: 25. Blood level: mice i.v., after 15 min. (γ/ml): 28.4.

## EXAMPLES 10 to 12

Synthesis of (3R,5R), (3R,5S) and (3S,5R) pyrrolidylthiocarbapenem derivatives




Step 1. Preparation of a protected pyrrolidylthiocarbapenem derivatives

To a solution of (1R,5S,6S)-2-diphenoxyphosphonyloxy-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid diphenylmethyl ester (i.e., a substrate) and 1-t-butoxycarbonyl-2-(N-t-butoxycarbonyl-N-sulfamoylamino)methyl-4-mercaptopyrrolidine (Pyld) in acetonitrile (MeCN) under ice cooling, diisopropylethylamine (HNPr-i) is added dropwise. The mixture is stirred to react under a condition shown in Table 4. The reaction mixture is diluted with ethyl acetate, and ice water is added thereto. The organic layer is taken, successively washed with water and saturated brine, dried over magnesium sulfate, and concentrated in vacuo. The residue is purified by silica gel chromatography to give (1R,5S,6S)-2-[1-t-butoxycarbonyl-5-(N-t-butoxycarbonyl-N-sulfamoylamino)methylpyrrolidin-3-yl]-thio-6-[(1R)-1-hydroxyethyl]-1-

methyl-1-carba-2-penem-3-carboxylic acid diphenylmethyl ester.

TABLE 4

| Example | Configuration of Pyld | Pyld[j] equiv. | HNPr-i[j] equiv. | MeCN[k] vol. | Temp. | Time min. | Yield % |
|---|---|---|---|---|---|---|---|
| Ex. 10 | 3R5R | 1.17 | 1.30 | 7 fold | ice cooling | 240 | 86 |
| Ex. 11 | 3R5S | 1.20 | 1.30 | 7 fold | ice cooling | 120 | 88 |
| Ex. 12 | 3S5R | 1.14 | 1.27 | 7 fold | ice cooling | 270 | 73 |

[i]Configuration of a pyrrolidine ring
[j]Molar ratio to the substrate
[k]The volume (ml) of the solvent to the weight (g) of the substrate

Physical properties of the products

(3R,5R) Isomer:

NMR δ($CDCl_3$) ppm: 1.26(d, J=7.2 Hz, 3H), 1.39(d, J=6.2 Hz, 3H), 1.43 (s, 9H), 1.51(s, 9H), 2.5(m, 1H), 3.1 to 3.9(m, 6H), 4.0 to 4.7(m, 4H), 6.1(m, 1H), 6.98(s, 1H), 7.1 to 7.6(m, 10H). IR ν (KBr) $cm^{-1}$: 3400, 3240, 1770, 1710, 1670.

(3S,5R) Isomer:

NMR δ($CDCl_3$) ppm: 1.28(d, J=7.0 Hz, 3H), 1.36(s, 9H), 1.40(d, J=6.2 Hz, 3H), 1.52(s, 9H), 2.0(m, 1H), 3.2 to 3.9(m, 7H), 4.2 to 4.4 (m, 2H), 4.4 to 4.6(m, 1H), 6.01(s, 2H), 6.94(s, 1H), 7.1 to 7.6(m, 10H). IR ν (KBr) $cm^{-1}$: 3400, 3240, 1772, 1708, 1682.

(3R,5S) Isomer:

NMR δ($CDCl_3$) ppm: 1.76(d, J=7.2 Hz, 3H), 1.3 to 1.5(m, 12H), 1.52(s, 9H), 1.9 to 2.1(m, 1H), 3.2 to 3.9(m, 7H), 4.1 to 4.4(m, 2H), 4.4 to 4.6(m, 1H), 6.04(s, 2H), 6.94(s, 1H), 7.1 to 7.6(m, 10H). IR ν (KBr) $cm^{-1}$: 3420, 1770, 1710.

Step 2. Deprotection

A solution of (1R,5S,6S)-2-[1-t-butoxycarbonyl-5-(N-t-butoxycarbonyl-N-sulfamoylamino)methylpyrrolidin-3-yl]thio-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid diphenylmethyl ester (i.e., a substrate) in dichloromethane (DCM) is added dropwise in a nitrogen atmosphere into a solution of aluminum chloride ($AlCl_3$) in a mixture of dichloromethane (DCM) and anisole (PhOMe). The mixture is stirred to react under the condition shown in Table 5. To the reaction mixture, aqueous sodium acetate is added. The aqueous layer is taken, washed with dichloromethane, and purified by column chromatography over styrenedivinylbenzene copolymer resin to give (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[5-sulfamidomethylpyrrolidin-3-yl]thio-1-methyl-1-carba-2-penem-3-carboxylic acid.

TABLE 5

| Example | Configuration[i] of Pyld | $AlCl_3$[m] equiv. | DCM[n] vol. (fold) | PhOMe[n] vol. (fold) | Temp. °C. | Time min. | Yield % |
|---|---|---|---|---|---|---|---|
| Ex. 10 | 3R5R | 8.0 | 16 | 10 | −30 | 300 | 86 |
| Ex. 11 | 3R5S | 8.0 | 17 | 10 | −30 | 150 | 88 |
| Ex. 12 | 3S5R | 8.0 | 17 | 10 | −30 | 150 | 73 |

[i]Configuration of a pyrrolidine ring
[m]Molar ratio to the substrate
[n]The volume (ml) of the solvent to the weight (g) of the substrate

Physical properties of the products

(3R,5R) Isomer:

NMR δ($D_2O$) ppm: 1.18(d, J=7.2 Hz, 3H), 1.27(d, J=6.2 Hz, 3H), 1.9(m, 1H), 2.7(m, 1H), 3.2 to 3.6(m, 5H), 3.6 to 3.8(m, 1H), 3.8 to 4.1(m, 2H), 4.2(m, 2H). IR ν (KBr) $cm^{-1}$: 3360, 1750.

(3S,5R) Isomer:

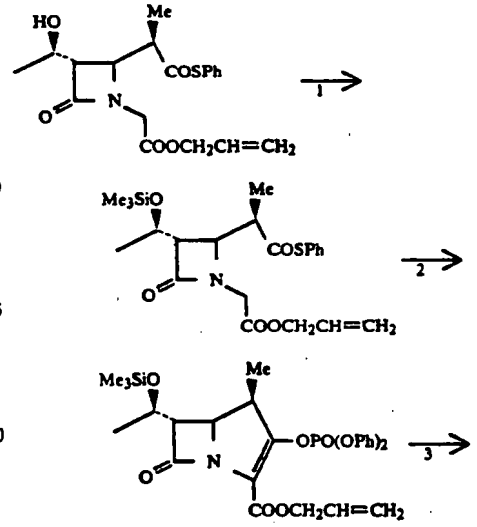
NMR δ($CD_3SOCD_3$) ppm: 1.09(d, J=7.0 Hz, 3H), 1.14(d, J=6.2 Hz, 3H), 1.7 to 2.0(m, 1H), 1.9 to 2.2(m, 1H), 2.9(m, 1H), 3.0 to 3.3(m, 4H), 3.3 to 3.6(m, 1H), 3.6 to 3.8(m, 2H), 3.9(m, 1H), 4.1(m, 1H). IR ν (KBr) $cm^{-1}$: 3340, 1765, 1740, 1620, 1575, 1548.

(3R,5S) Isomer:

NMR δ($D_2O$) ppm: 0.86(d, J=7.4 Hz, 3H), 0.93(d, J=6.4 Hz, 3H), 2.43(d, J=6.4 Hz, 3H), 1.90(dd, J=9.0 Hz, J=4.4 Hz, 2H), 2.9 to 3.3(m, 5H), 3.48(dd, J=13.2 Hz, J=7.2 Hz, 1H), 3.7 to 3.8(m, 2H), 3.8 to 4.0 (m, 2H), 4.47 DHO. IR ν (KBr) $cm^{-1}$: 3400, 1750, 1585.

EXAMPLE 13

Synthesis of a (3S,5S)-pyrrolidylthiocarbapenem derivative using a monoallyloxycarbonyl intermediate



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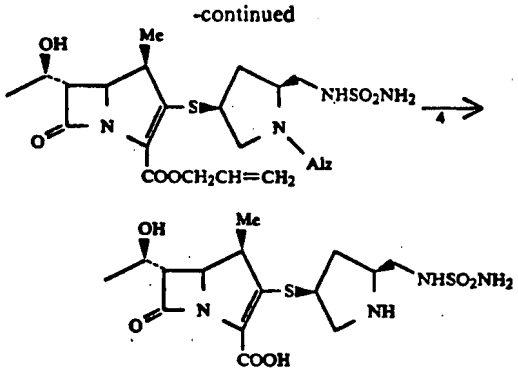


Step 1. Preparation of a trimethylsilyl compound

To a solution of (3S,4S)-3-[(1R)-1-hydroxyethyl]-4-[(1R)-1-phenylthiocarbonylethyl]-1-allyloxycarbonylmethyl-2-azetidinone (5.04 g: 13.35 mmole) in toluene (40 ml) under ice cooling, pyridine (1.51 ml: 18.69 mmole) is added and trimethylchlorosilane (2.26 ml: 17.36 mmole) is added dropwise. The mixture is stirred at room temperature for 1.5 hours. Water (80 ml) is added to the reaction mixture, and aqueous layer is extracted with toluene. The extract and the organic layer are combined, washed with water (2 times) and saturated brine, dried over magnesium sulfate, and concentrated in vacuo to give crude (3S,4S)-3-[(1R)-1-trimethylsilyloxyethyl]-4-[(1R)-1-phenylthiocarbonylethyl]-1-allyloxycarbonylmethyl-2-azetidinone (5.614 g) as oily residue. Yield: 94%.

Step 2. Ring closure

To a solution of the crude (3S,4S)-3-[(1R)-1-trimethylsilyloxyethyl]-4-[(1R)-1-phenylthiocarbonylethyl]-1-allyloxycarbonylmethyl-2-azetidinone (5.60 g: 12.454 mmole) obtained in Step 1 in tetrahydrofuran 62 ml) at −60° C., a solution of 1M-potassium t-butoxide (24.9 mmole) in tetrahydrofuran (24.9 ml) is added dropwise. The mixture is stirred for 10 minutes. After adding iodomethane (0.48 ml: 14.94 mmole) and stirring at the same temperature for 20 minutes, diphenylphosphoryl chloride (2.73 ml: 12.45 mmole) is added thereto. After allowing to warm to an ice water temperature over 1 hour, the reaction mixture is diluted with toluene (120 ml) and water (120 ml). The aqueous layer is extracted with toluene. The extract and the organic layer are combined, successively washed with water (2 times), aqueous sodium hydrogen carbonate, and saturated brine, dried over magnesium sulfate, and concentrated in vacuo to give crude (1R,5S,6S)-2-diphenoxyphospholyloxy-6-[(1R)-1-trimethylsilyloxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid allyl ester (3.795 g) as oily residue. Yield: 104%. IR $\nu$ ($CHCl_3$) $cm^{-1}$: 3008, 1778, 1722, 1636, 1589, 1489. NMR $\delta$($CDCl_3$) ppm: 0.12(9H, s), 1.19(3H, d, J=7.2 Hz), 1.25(3H, d, J=6.2 Hz), 3.24(1H, dd, J=3.0 Hz, J=6.8 Hz), 3.3 to 3.6(1H, m), 4.11(1H, dd, J=3.0 Hz, J=10.2 Hz), 4.1 to 4.3(1H, m), 4.6 to 4.7(2H, m), 5.1 to 5.5(2H, m), 5.7 to 6.0(1H, m), 7.1 to 7.5(10H, m).

Step 3. Preparation of a protected pyrrolidylthiocarbapenem derivative

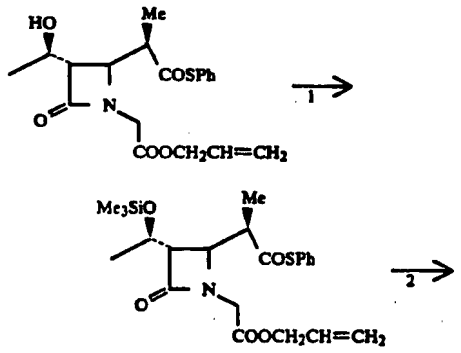
To a solution of crude (1R,5S,6S)-2-diphenoxy-phospholyloxy-6-[(1R)-1-trimethylsilyloxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid allyl ester (2.56 g: 4.2 mmole) obtained in Step 2 and (2S,4S)-1-allyloxycarbonyl-2-(N-sulfamoylamino)methyl-4-mercaptopyrrolidine (1.48 g: 5.0 mmole) in acetonitrile (13 ml) under ice cooling, diisopropylethylamine (0.95 ml: 5.46 mmole) is added dropwise, and the mixture is stirred at the same temperature for 7.5 hours. The reaction mixture is acidified with 1N-hydrochloric acid (6.3 ml), stirred at the same temperature for 30 minutes, and ethyl acetate (80 ml) and ice water (80 ml) are added thereto. The organic layer is taken, successively washed with water and saturated brine, dried over magnesium sulfate and concentrated in vacuo. The residue is purified by silica gel chromatography (toluene-ethyl acetate) to give (1R,5S,6S)-2-[(3S,5S)-1-allyloxycarbonyl-5-(N-sulfamoylamino)methyl-pyrrolidin-3-yl]thio-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid allyl ester (1.63 g). Yield: 71%. IR $\nu$ ($CHCl_3$) $cm^{-1}$: 1772, 1691, 1410. $^1$HNMR $\delta$($CDCl_3$) ppm: 1.26(3H, d, J=7.0 Hz), 1.35(3H, d, J=6.0 Hz), 1.7 to 2.7(3H, m), 3.1 to 3.5(5H, m), 3.5 to 3.8(1H, m), 3.9 to 4.4(4H, m), 4.5 to 4.9 (4H, m), 5.0 to 5.5(5H, m), 5.8 to 6.1(2H, m).

Step 4. Deprotection

To a solution of (1R,5S,6S)-2-[(3S,5S)-1-allyloxycarbonyl-5-(N-sulfamoylamino) methylpyrrolidin-3-yl]thio-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid allyl ester (379 mg: 0.695 mmole) in acetone (14 ml), triphenylphosphine (55 mg: 0.21 mmole) and tri-n-butyltin hydride (0.424 ml: 1.53 mmole) are added. Under ice cooling palladium tetrakis(triphenylphosphine) (81 mg: 0.07 mmole) is further added. After stirring at the same temperature for 45 minutes and at room temperature for 1 hour, water (35 ml) and methylene chloride (50 ml) are added to the reaction mixture. The aqueous layer is taken, washed with methylene chloride and lyophilized to give (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(3S,5S)-5-sulfamidomethylpyrrolidin-3-yl]thio-1-methyl-1-carba-2-penem-3-carboxylic acid (238 mg). Yield: 82%. (HPLC purity: 85%) NMR $\delta(D_2O)$ ppm: 1.22(d, J=7.2 Hz, 3H), 1.27(d, J=6.3 Hz, 3H), 1.64 to 1.82(m, 1H), 2.62 to 2.80(m, 1H), 3.26 to 3.59(m, 5H), 3.63 to 3.76(m, 1H), 3.84 to 4.10(m, 2H), 4.16 to 4.29(m, 2H). IR $\nu$ (KBr) $cm^{-1}$: 1340, 1750.

## EXAMPLE 14

Synthesis of a (3S,5S)-pyrrolidylthiocarbapenem derivative using a diallyloxycarbonyl intermediate



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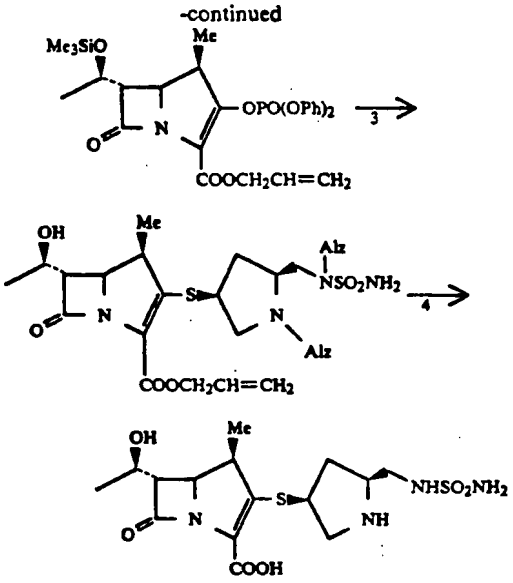


Step 1. Preparation of a trimethylsilyl compound

(3S,4S)-3-[(1R)-1-hydroxyethyl]-4-[(1R)-1-phenylthiocarbonylethyl]-1-allyloxycarbonylmethyl-2-azetidinone is trimethylsilylated in the same manner as in Step 1 in Example 13 to give (3S,4S)-3-[(1R)-1-trimethylsilyloxyethyl]-4-[(1R)-1-phenylthiocarbonylethyl]-1-allyoxycarbonylmethyl-2-azetidinone.

Step 2. Ring closure

The crude (3S,4S)-3-[(1R)-1-trimethylsilyloxyethyl]-4-[(1R)-1-phenylthiocarbonylethyl]-1-allyloxy-carbonylmethyl-2-azetidinone obtained in Step 1 is allowed to react to close the ring in the similar manner as in Step 2 of Example 13 to give crude (1R,5S,6S)-2-diphenoxyphosphoryloxy-6-[(1R)-1-trimethylsilyloxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid allyl ester.

Step 3 Preparation of a protected pyrrolidylthio carbapenem derivative

Under similar reaction condition, the crude (1R,5S,6S)-2-diphenoxyphosphoryloxy-6-[(1R)-1-trimethylsilyloxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid allyl ester (5.05 g: 8.3 mmole) obtained in Step 2 and (2S,4S)-1-allyloxycarbonyl-2-(N-allyloxycarbonyl-N-sulfamoylamino)methyl-4-mercaptopyrrolidine (3.77 g: 9.94 mmole) are reacted to give (1R,5S,6S)-2-[(3S,5S)-1-allyloxycarbonyl-5-(N-allyloxycarbonyl-N-sulfamoylamino)methylpyrrolidin-3-yl]thio-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid allyl ester (3.65 g). Yield: 70%. IR $\nu$ ($CHCl_3$) $cm^{-1}$: 1777, 1718, 1686, 1395. NMR $\delta$($CDCl_3$) ppm: 1.27(3H, d, J=7.2 Hz), 1.37(3H, d, J=6.2 Hz), 2.5 to 2.7(1H, m), 3.1 to 3.3(3H, m), 3.6 to 3.8(2H, m), 4.0 to 4.3(4H, m), 4.4 to 4.9 (6H, m), 5.2 to 5.5(6H, m), 5.7 to 6.1(5H, m).

Step 4 Deprotection

Under similar reaction condition to that in Step 4 in Example 13, (1R,5S,6S)-2-[(3S,5S)-1-allyloxycarbonyl-5-(N-allyloxycarbonyl-N-sulfamoylamino)methylpyrrolidin-3-yl]thio-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid allyl ester (369 mg: 0.586 mmole) is deprotected with triphenylphosphine (83 mg: 0.32 mmole), tri-n-butyltin hydride (0.64 ml: 2.3 mmole), and palladium tetrakis(triphenylphosphine) (122 mg: 0.11 mmole) to give (1R, 5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(3S,5S)-5-sulfamidomethylpyrrolidin-3-yl]thio-1-methyl-1-carba-2-penem-3-carboxylic acid (206 mg). Yield: 84%. (HPLC purity: 85%) NMR $\delta$(D2O) ppm: 1.22(d, J=7.2 Hz, 3H), 1.27(d, J=6.3 Hz, 3H), 1.64 to 1.82(m, 1H), 2.62 to 2.80(m, 1H), 3.26 to 3.59(m, 5H), 3.63 to 3.76(m, 1H), 3.84 to 4.10(m, 2H), 4.16 to 4.29(m, 2H). IR $\nu$ (KBr) $cm^{-1}$: 3400, 1750.

## EXAMPLE 15

A solution of (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(3S,5S)-5-sulfamidomethylphrrolidin-3-yl]thio-1-methyl-1-carba-2-penem-3-carboxylic acid (0.5 g) in aqueous sodium hydrogen carbonate (5 ml) at pH 7.0 is filled in a vial (10 ml) and lyophilized. The lyophilizate is dissolved in water for infection (5 ml) before use and injected thrice a day intravenously to a patient suffering from urinary tract infection caused by a sensitive strain of *Staphylococcus aureus* to cure the disease.

## EXAMPLE 16

A solution of (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(3S,5S)-5-(methylsulfamoyl)aminomethylpyrrolidin-3-yl]thio-1-methyl-1-carba-2-penem-3-carboxylic acid (0.5 g) in aqueous sodium hydrogen carbonate (5 ml) at pH 7.0 is filled in a vial (10 ml) and lyophilized. The lyophilizate is dissolved in water for infection (5 ml) before use and injected thrice a day intravenously to a patient suffering from pneumonia caused by a sensitive strain of *Klebsiella pneumoniae* to treat the disease.

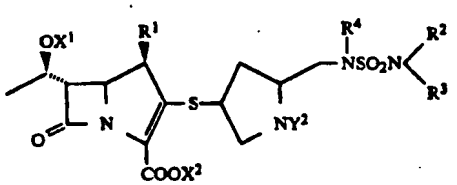
## EXAMPLE 17

A solution of (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(3S,5S)-5-(2-hydroxyethylsulfamoyl)aminomethylpyrrolidin-3-yl]thio-1-methyl-1-carba-2-penem-3-carboxylic acid (2.0 g) in aqueous sodium hydrogen carbonate (10 ml) at pH 7.0 is filled in vial (100 ml) and lyophilized. The lyophilizate is dissolved in water for injection (50 ml) before use and administered by infusion four times a day intravenously to a patient severely suffering from the respiratory tract infection caused by a sensitive strain of *Enterobacter cloacae* to cure the disease.

Various other modifications will be apparent to and can be readily made by those skilled in the art without departing from the scope and spirit of this invention. Accordingly, it is not intended that the scope of the claims appended hereto be limited to the description as set forth herein, but rather that the claims be broadly construed.

What is claimed is:

1. A pyrrolidylthiocarbapenem derivative represented by Formula I:



(I)

wherein $R^1$ is hydrogen or lower alkyl; $R^2$, $R^3$ and $R^4$ are hydrogen, lower alkyl which can be substituted, or an amino protecting group independently, or $R^2$ and $R^3$ together with a nitrogen atom to

which $R^2$ and $R^3$ are bonded form a saturated or unsaturated cyclic group, or $R^2$ and $R^4$, or $R^3$ and $R^4$ together with two nitrogen atoms and one sulfur atom in the sulfamide group form a saturated or unsaturated cyclic group; each cyclic group can further include at least one atom selected from the group consisting of oxygen, sulfur and nitrogen, and each cyclic group can be substituted; $X^1$ is hydrogen or a hydroxy protecting group; $X^2$ is hydrogen, a carboxy protecting group, an ammonio group, an alkali metal or an alkaline-earth metal; and $Y^2$ is hydrogen or an amino protecting group.

2. A pyrrolidylthiocarbapenem derivative according to claim 1, wherein $R^1$ is methyl.

3. A pyrrolidylthiocarbapenem derivative according to claim 2, wherein $R^4$ is hydrogen.

4. A pyrrolidylthiocarbapenem derivative according to claim 3, wherein $X^1$ and $Y^2$ are hydrogens and $X^2$ is hydrogen or alkali metal.

5. A pyrrolidylthiocarbapenem derivative according to claim 4, wherein $R^2$ and $R^3$ are hydrogens; $R^2$ is methyl and $R^3$ are hydrogen; both $R^2$ and $R^3$ are methyl; or $R^2$ is 2-hydroxyethyl, and $R^3$ are hydrogen.

6. A pyrrolidylthiocarbapenem derivative according to claim 2, wherein $R^3$ is hydrogen, and $R^2$ and $R^4$ are bonded to each other to form $-CH_2-CH_2-$.

7. A pyrrolidylthiocarbapenem derivative according to claim 2, wherein $R^3$ is hydrogen, and $R^2$ and $R^4$ are bonded to each other to form $-CH_2-CH_2-CH_2-$.

8. A pyrrolidylthiocarbapenem derivative according to claim 1, wherein at least one group selected from the group consisting of $R^2$, $R^3$, $R^4$ and $Y^2$ is selected from the group consisting of t-butyloxy carbonyl, allyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl and diazo.

9. A pyrrolidylthiocarbapenem derivative according to claim 1, wherein $X^1$ is selected from the group consisting of hydrogen, trimethylsilyl, triethylsilyl and t-butoxydimethylsilyl.

10. A pyrrolidylthiocarbapenem derivative according to claim 1, wherein $X^2$ is selected from the group consisting of hydrogen, sodium potassium, t-butyl, allyl, p-nitrobenzyl, p-methoxybenzyl and diphenylmethyl.

11. A pyrrolidylthiocarbapenem derivative according to claim 1, wherein the pyrrolidine ring in Formula I has a configulation of (3S,5S).

12. An antibacterial agent comprising an effective amount of the pyrrolidylthiocarbapenem derivative of claim 1 as an active ingredient.

13. An antibacterial agent comprising an effective amount of the pyrrolidylthiocarbapenem derivative of claim 4 as an active ingredient.

14. An antibacterial agent comprising an effective amount of the pyrrolidylthiocarbapenem derivative of claim 5 as an active ingredient.

15. An antibacterial agent comprising an effective amount of the pyrrolidylthiocarbapenem derivative of claim 11 as an active ingredient.

16. A method for inhibiting growth of bacteria sensitive to the pyrrolidylthiocarbapenem derivative of claim 1 by allowing the sensitive bacterium to be in contact with an effective amount of the pyrrolidylthiocarbapenem derivative.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO. : 5,317,016

DATED : May 31, 1994

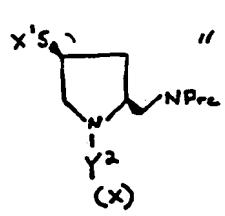
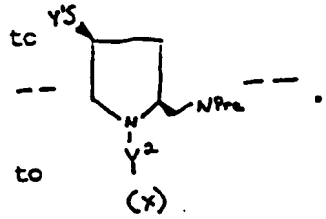
INVENTOR(S) : Yasuhiro Nishitani, et al.

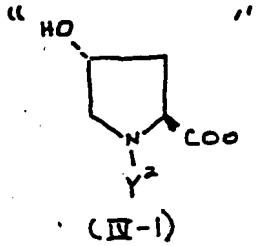
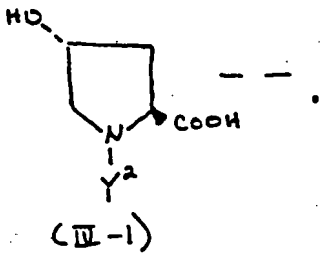


It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Title Page, Inventors, Change "Yasuhiro Nishitani; Tadashi; Irie, both of Osaka, Japan" to —Yasuhiro Nishitani, Tadashi Irie, Yutaka Nishino, all of Osaka, Japan—.

Column 8:
Line 60, change "(VIII)" to —(VII)—.

Column 9, lines 60–67, change "  " to 

Column 10, lines 54–60, change "  " to 

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO. : 5,317,016

DATED : May 31, 1994

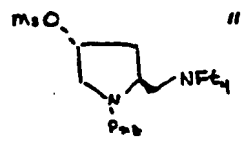
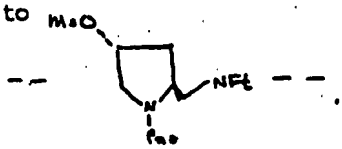
INVENTOR(S) : Yasuhiro Nishitani, et al.

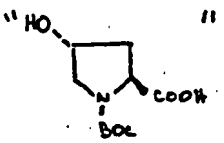
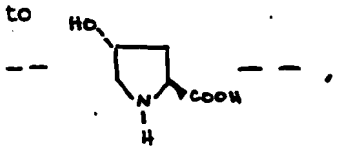


It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Column 17, line 43, after "83.5" and before "." please insert —%—.

Column 22, line 49, change "435" to —45—.

Column 24, lines 1-5, change "  " to  .

Column 40, lines 44-49, change "  " to  .

Column 42, line 48, change "(2S,4)" to —(2S,4S)—.

Column 55, line 13, delete "-nyl".

Column 57, line 63, after "(2" and before "-" delete ")".

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO. : 5,317,016 

DATED : May 31, 1994

INVENTOR(S) : Yasuhiro Nishitani and Tadashi Irie

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 59, line 56, change "65%" to —64%—.

Column 63, line 39, before "62" insert —(—.

Claim 10, column 68, line 11, after "sodium" and before "potassium" insert —,—.

Signed and Sealed this

First Day of November, 1994

Bruce Lehman

BRUCE LEHMAN

*Attest:*

*Attesting Officer*

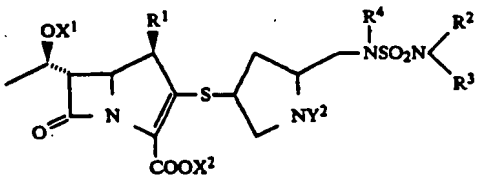
*Commissioner of Patents and Trademarks*

Exhibit 4

**Claims 1-5 and 9-16 of U.S. Patent No. 5,317,016 Read on the Active Ingredient, a Composition and a Method of Using the Approved Product**

What is claimed is:

1. A pyrrolidylthiocarbapenem derivative represented by Formula I:



(I)

wherein $R^1$ is hydrogen or lower alkyl; $R^2$, $R^3$ and $R^4$ are hydrogen, lower alkyl which can be substituted, or an amino protecting group independently, or $R^2$ and $R^3$ together with a nitrogen atom to which $R^2$ and $R^3$ are bonded form a saturated or unsaturated cyclic group, or $R^2$ and $R^4$, or $R^3$ and $R^4$ together with two nitrogen atoms and one sulfur atom in the sulfamide group form a saturated or unsaturated cyclic group; each cyclic group can further include at least one atom selected from the group consisting of oxygen, sulfur and nitrogen, and each cyclic group can be substituted; $X^1$ is hydrogen or a hydroxy protecting group; $X^2$ is hydrogen, a carboxy protecting group, an ammonio group, an alkali metal or an alkaline-earth metal; and $Y^2$ is hydrogen or an amino protecting group.

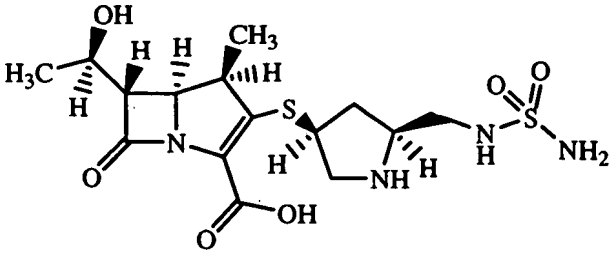
2. A pyrrolidylthiocarbapenem derivative according to claim 1, wherein $R^1$ is methyl.

3. A pyrrolidylthiocarbapenem derivative according to claim 2, wherein $R^4$ is hydrogen.

4. A pyrrolidylthiocarbapenem derivative according to claim 3, wherein $X^1$ and $Y^2$ are hydrogens and $X^2$ is hydrogen or alkali metal.

5. A pyrrolidylthiocarbapenem derivative according to claim 4, wherein $R^2$ and $R^3$ are hydrogens; $R^2$ is methyl and $R^3$ are hydrogen; both $R^2$ and $R^3$ are methyl; or $R^2$ is 2-hydroxyethyl, and $R^3$ are hydrogen.

The chemical structure of DORIBAX™ is:



Claim 1- Doripenem is claimed in claim 1, specifically when the variable moieties are as follows: when $R_1$ is lower alkyl; $R_2$, $R_3$, and $R_4$ are all hydrogen; $X_1$ is hydrogen; $X_2$ is hydrogen; and $Y_2$ is hydrogen.

Doripenem is covered explicitly by the Formula I structure. The only substituent moiety other than hydrogen is $R_1$. "Lower alkyl" is defined in the '016 patent specification at column 4, lines 1-6. Specifically at column 4, lines 5-6- "The most preferred lower alkyl is methyl or ethyl."

Claim 2- Doripenem is claimed in claim 2 when $R_1$ is methyl.

Claim 3- Doripenem is claimed in claim 3 when $R_1$ is methyl and $R_4$ is hydrogen.

Claim 4- Doripenem is claimed in claim 4 when $R_1$ is methyl $R_4$ is hydrogen, and $X_1$, $X_2$ and $Y_2$ are all hydrogen.

| | |
|---|---|
| **9.** A pyrrolidylthiocarbapenem derivative according to claim **1**, wherein $X^1$ is selected from the group consisting of hydrogen, trimethylsilyl, triethylsilyl and t-butoxydimethylsilyl.<br>**10.** A pyrrolidylthiocarbapenem derivative according to claim **1**, wherein $X^2$ is selected from the group consisting of hydrogen, sodium potassium, t-butyl, allyl, p-nitrobenzyl, p-methoxybenzyl and diphenylmethyl.<br>**11.** A pyrrolidylthiocarbapenem derivative according to claim **1**, wherein the pyrrolidine ring in Formula I has a configulation of (3S,5S).<br><br>**12.** An antibacterial agent comprising an effective amount of the pyrrolidylthiocarbapenem derivative of claim **1** as an active ingredient.<br>**13.** An antibacterial agent comprising an effective amount of the pyrrolidylthiocarbapenem derivative of claim **4** as an active ingredient.<br>**14.** An antibacterial agent comprising an effective amount of the pyrrolidylthiocarbapenem derivative of claim **5** as an active ingredient.<br>**15.** An antibacterial agent comprising an effective amount of the pyrrolidylthiocarbapenem derivative of claim **11** as an active ingredient.<br>**16.** A method for inhibiting growth of bacteria sensitive to the pyrrolidylthiocarbapenem derivative of claim **1** by allowing the sensitive bacterium to be in contact with an effective amount of the pyrrolidylthiocarbapenem derivative. | Claim 5- Doripenem is claimed in claim 5 when $R_1$ is methyl, and $X_1$, $X_2$, $Y_2$, $R_2$ and $R_3$ are hydrogen.<br><br>Claim 9- Doripenem is claimed in claim 9 when $X_1$ is hydrogen.<br><br>Claim 10- Doripenem is Claimed in claim 10 when $X_2$ is hydrogen.<br><br>Claim 11- Doripenem is claimed in claim 11 because the pyrrolidine ring has the (3S,5S) configuration.<br><br>Claims 12-15- Claim the composition of the active ingredient doripenem.<br><br>Claim 16- Claims a method of using doripenem |

**Exhibit 3**

**Copy of U.S. Patent & Trademark Office Maintenance Fee Statements for U.S. Patent No. 5,317,016**

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10/16/2007

RENNER, OTTO, BOISELLE & SKLAR
ATTN: PAM GOFORTH
1621 EUCLID AVENUE
NINETEENTH FLOOR

# MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

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Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

| PATENT NUMBER | FEE AMT | SUR CHARGE | PYMT DATE | U.S. APPLICATION NUMBER | PATENT ISSUE DATE | APPL. FILING DATE | PAYMENT YEAR | SMALL ENTITY? | ATTY DKT NUMBER |
|---|---|---|---|---|---|---|---|---|---|
| 5,317,016 | $1,050.00 | $0.00 | 11/03/97 | 07/929,961 | 05/31/94 | 08/14/92 | 04 | NO | YAMA-113 |

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The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

| PATENT NUMBER | FEE AMT | SUR CHARGE | PYMT DATE | U.S. APPLICATION NUMBER | PATENT ISSUE DATE | APPL. FILING DATE | PAYMENT YEAR | SMALL ENTITY? | ATTY DKT NUMBER |
|---|---|---|---|---|---|---|---|---|---|
| 5,317,016 | $2,020.00 | $0.00 | 10/25/01 | 07/929,961 | 05/31/94 | 08/14/92 | 08 | NO | YAMA-113 |

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# MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

| PATENT NUMBER | FEE AMT | SUR CHARGE | PYMT DATE | U.S. APPLICATION NUMBER | PATENT ISSUE DATE | APPL. FILING DATE | PAYMENT YEAR | SMALL ENTITY? | ATTY DKT NUMBER |
|---|---|---|---|---|---|---|---|---|---|
| 5,317,016 | $3,800.00 | $0.00 | 11/04/05 | 07/929,961 | 05/31/94 | 08/14/92 | 12 | NO | YAMA-113 |

# EXHIBIT 5

## DESCRIPTION OF SIGNIFICANT ACTIVITIES OF APPLICANT DURING REGULATORY REVIEW

### IND 64,416 (Doripenem) US Submission Log

| Date | Serial Number | Submission |
|---|---|---|
| 9/20/2002 | n/a | General Correspondence: Submitted Pre-IND Briefing Package |
| 10/3/2002 | n/a | FDA Correspondence: Letter: Confirmation of receipt of Pre-IND package; assignment of pre-IND number. |
| 11/21/2002 | n/a | FDA Correspondence |
| 11/21/2002 | n/a | FDA Correspondence |
| 12/2/2002 | 000 | Original Application SN 000 Vol.. 1 through 14 |
| 12/3/2002 | n/a | Response to FDA Request For Information |
| 12/13/2002 | n/a | Response to FDA Request For Information |
| 12/20/2002 | n/a | FDA Correspondence |
| 12/20/2002 | n/a | FDA Correspondence |
| 12/26/2002 | n/a | Response to FDA Request For Information |
| 12/30/2002 | n/a | Response to FDA Request For Information |
| 1/2/2003 | n/a | FDA Correspondence |
| 1/2/2003 | 001 | General Correspondence |
| 1/6/2003 | n/a | FDA Correspondence |
| 1/22/2003 | 002 | General Correspondence |
| 1/23/2003 | n/a | FDA Correspondence |
| 1/29/2003 | n/a | General Correspondence |
| 2/26/2003 | 003 | Protocol Amendment: New Investigator(s) – DORI-03 |
| 2/26/2003 | 004 | Information Amendment - Pharmacology/Toxicology |
| 3/6/2003 | 005 | Protocol Amendment: Change in Protocol - DORI-03, Amendment 3. |
| 3/6/2003 | 006 | Information Amendment - Pharmacology/Toxicology |
| 3/11/2003 | n/a | FDA Correspondence |
| 3/27/2003 | 007 | Protocol Amendment: New Investigator(s) – DORI-03 |
| 3/27/2003 | 008 | Information Amendment - Pharmacology/Toxicology |
| 4/9/2003 | 009 | Protocol Amendment: New Protocol – DORI-04 |
| 4/9/2003 | 010 | Information Amendment - CMC |
| 5/1/2003 | 011 | Protocol Amendment: New Investigator(s) – DORI-03 |
| 5/7/2003 | n/a | FDA Correspondence |
| 5/8/2003 | 012 | Response to FDA Request For Information |
| 5/28/2003 | 013 | Protocol Amendment: New Investigator – DORI-03 |
| 5/28/2003 | 014 | General Correspondence - Pharmacology/Toxicology |

*Duplicate IND serial number inadvertently submitted.

| Date | Serial Number | Submission |
|---|---|---|
| 6/12/2003 | 015 | General Correspondence |
| 6/12/2003 | 016 | Protocol Amendment: Change in Protocol – DORI-03, Amendment 4. |
| 7/3/2003 | 017 | Safety Report: Initial Report |
| 7/8/2003 | 018 | Protocol Amendment: New Investigator(s) – DORI-03 |
| 7/29/2003 | 019 | Safety Report: Follow-up Report |
| 7/29/03 | 020 | General Correspondence - Pharmacology/Toxicology |
| 8/7/2003 | 021 | Information Amendment - CMC |
| 8/8/2003 | n/a | FDA Correspondence |
| 8/27/2003 | 022 | Protocol Amendment: Change in Protocol – DORI-03 |
| 08/27/03 | 023 | Information Amendment - Pharmacology/Toxicology |
| 09/24/03 | 024 | General Correspondence |
| 10/9/2003 | n/a | FDA Correspondence |
| 10/13/2003 | 025 | General Correspondence |
| 11/6/2003 | n/a | FDA Correspondence |
| 11/7/2003 | 026 | General Correspondence: Meeting Request |
| 11/7/2003 | 027 | General Correspondence |
| 11/12/2003 | n/a | FDA Correspondence |
| 11/17/2003 | n/a | FDA Correspondence |
| 11/17/2003 | n/a | FDA Correspondence |
| 11/21/2003 | n/a | FDA Correspondence |
| 11/25/2003 | 028 | General Correspondence: Meeting Briefing Document |
| 11/26/2003 | 029 | General Correspondence: Meeting Request |
| No Date | n/a | General Correspondence |
| 12/5/2003 | n/a | FDA Correspondence |
| 12/8/2003 | n/a | General Correspondence |
| 12/8/2003 | n/a | General Correspondence |
| 12/08/2003 | 030 | General Correspondence: Meeting Briefing Package |
| 12/11/2003 | n/a | FDA Correspondence |
| 12/17/2003 | 031 | Protocol Amendment: New Investigator – DORI-05 |
| 12/18/2003 | 032 | General Correspondence |
| 12/18/2003 | 033 | Information Amendment - CMC |
| 12/19/2003 | n/a | General Correspondence |
| 12/23/2003 | 034 | Response to FDA Request For Information |
| 12/24/2003 | 035 | General Correspondence: Type C Meeting Request |
| 1/5/2004 | 036 | Information Amendment - Pharmacology/Toxicology reports |
| 1/12/2004 | 037 | General Correspondence |
| 1/12/2004 | n/a | FDA Correspondence |
| 1/14/2004 | n/a | FDA Correspondence |
| 1/15/2004 | 038 | Information Amendment - Pharmacology/Toxicology |
| 1/16/2004 | 039 | Protocol Amendment: New Investigator – DORI-05 |
| 1/23/2004 | n/a | FDA Correspondence |

*Duplicate IND serial number inadvertently submitted.

| Date | Serial Number | Submission |
|---|---|---|
| 01/27/04 | 040 | Information Amendment: Clinical Study Report – DORI-01 |
| 02/05/04 | 041 | General Correspondence |
| 2/11/2004 | 042 | Protocol Amendment: Change in Protocol – DORI-05 |
| 2/13/2004 | n/a | FDA Correspondence |
| 2/18/2004 | 043 | Annual Report: 2 December 2002 - 1 December 2003 |
| 2/18/2004 | 044 | General Correspondence: Meeting Request |
| 2/19/2004 | 045 | Protocol Amendment: New Protocol – DORI-06 |
| 2/19/2004 | 046 | Protocol Amendment: New Protocol – DORI-07 |
| 2/19/2004 | 047 | Protocol Amendment: New Protocol – DORI-08 |
| 2/20/2004 | 048 | Information Amendment: Clinical Study Report – DORI-02 |
| 2/20/2004 | 049 | Information Amendment: Clinical Study Report – DORI-04 |
| 2/26/2004 | n/a | FDA Correspondence |
| 3/2/2004 | n/a | FDA Correspondence |
| 3/3/2004 | n/a | FDA Correspondence |
| 3/3/2004 | n/a | General Correspondence |
| 3/4/2004 | n/a | FDA Correspondence |
| 3/9/2004 | n/a | Response to FDA Request For Information |
| 03/9/04 | 050 | Protocol Amendment: New Investigator(s) – DORI-07 |
| 3/12/2004 | 051 | Protocol Amendment: New Investigator(s) – DORI-05 |
| 3/12/2004 | 052 | Protocol Amendment: New Investigator(s) – DORI-06 |
| 3/15/2004 | 053 | Information Amendment: Clinical Study Report – DORI-03 |
| 03/18/04 | 054 | General Correspondence |
| 3/19/2004 | 055 | Protocol Amendment: New Investigator(s) – DORI-08 |
| 3/24/2004 | 056 | General Correspondence |
| 3/24/04 | n/a | FDA Correspondence |
| 3/26/2004 | 057 | General Correspondence |
| 4/01/04 | 058 | General Correspondence: Meeting Briefing Package |
| 4/6/2004 | n/a | Response to FDA Request For Information |
| 4/6/2004 | 059 | Information Amendment - Clinical |
| 4/8/2004 | 060 | Response to FDA Request For Information |
| 4/9/2004 | n/a | FDA Correspondence |
| 4/12/2004 | 061 | Response to FDA Request For Information |
| 4/14/2004 | 062 | Response to FDA Request For Information |
| 4/23/04 | 063 | Information Amendment - Clinical |
| 4/22/04 | 064 | Protocol Amendment: New Investigator – DORI-05 |
| 4/23/04 | 065 | Response to FDA Request for Information |
| 4/23/04 | 066 | Protocol Amendment: New Investigator(s) – DORI-05 |

*Duplicate IND serial number inadvertently submitted.

| Date | Serial Number | Submission |
|---|---|---|
| 4/23/04 | 067 | Protocol Amendment: New Investigator(s) – DORI-06 |
| 4/26/2004 | 068 | Response to FDA Request For Information |
| 4/28/2004 | 069 | Information Amendment - Chemistry/Microbiology |
| 4/30/2004 | n/a | FDA Correspondence |
| 5/14/2004 | 070 | General Correspondence |
| 6/2/2004 | 071 | Protocol Amendment: New Investigator(s) - DORI-09 |
| 6/2/2004 | n/a | FDA Correspondence |
| 6/4/2004 | 072 | Protocol Amendment: New Investigator(s) - DORI-05 |
| 06/16/2004 | 073 | Protocol Amendment: New Investigator(s) - DORI-10 |
| 6/17/2004 | 074 | General Correspondence |
| 6/21/2004 | 075 | General Correspondence: Meeting Request |
| 6/29/2004 | n/a | FDA Correspondence |
| 6/15/2004 | n/a | General Correspondence |
| 6/21/2004 | 076 | Response to FDA Request For Information |
| 8/2/2004 | 077 | General Correspondence |
| 8/5/2004 | n/a | FDA Correspondence |
| 8/10/2004 | 078 | Safety Report: Initial |
| 8/31/2004 | 079 | Safety Report: Initial |
| 9/15/2004 | 080 | Protocol Amendment: Change in Protocol DORI-05 |
| 9/22/2004 | 081 | Protocol Amendment: Change in Protocol DORI-07 |
| 09/22/2004 | 082 | General Correspondence |
| 9/24/2004 | 083 | Information Amendment - Pharmacology/Toxicology |
| 9/27/2004 | 084 | Safety Report: Follow-up |
| 9/28/2004 | 085 | General Correspondence |
| 10/6/2004 | 086 | Information Amendment - Pharmacology/Toxicology |
| 10/18/2004 | n/a | FDA Correspondence |
| 10/21/2004 | 087 | Information Amendment - Pharmacology/Toxicology |
| 11/9/2004 | 088 | Safety Report: Follow-up |
| 11/30/04 | 089 | Protocol Amendment: Change in Protocol DORI-09 |
| 12/3/2004 | 090 | Safety Report: Follow up |
| 1/7/2005 | 091 | Safety Report: Initial |
| 1/10/2005 | 092 | Information Amendment - Clinical |
| 1/19/2005 | 093 | General Correspondence |
| 1/20/2005 | 094 | Protocol Amendment: New Investigator(s) - DORI-06 |
| 1/31/2005 | 095 | Protocol Amendment: New Investigator(s) - DORI-05 |
| 1/31/2005 | 096 | General Correspondence |
| 2/03/05 | 097 | Protocol Amendment: New Investigator(s) - DORI-06 |
| 2/7/2005 | 098 | Safety Report: Follow up |
| 2/7/2005 | 099 | Protocol Amendment: New Investigator(s) - DORI-07 |

*Duplicate IND serial number inadvertently submitted.

| Date | Serial Number | Submission |
|---|---|---|
| 2/9/2005 | 100 | Protocol Amendment: New Investigator(s) - DORI-08 |
| 2/11/05 | 101 | Annual Report: December 2, 2003 - December 1, 2004 |
| 2/14/2005 | 102 | Protocol Amendment: New Investigator(s) - DORI-09 |
| 2/17/2005 | 103 | Protocol Amendment: New and updated Investigator(s) - DORI-10 |
| 2/17/2005 | n/a | FDA Correspondence |
| 2/21/05 | 104 | Protocol Amendment: Change in Protocol - DORI-10, Amendment 1 |
| 3/1/2005 | 105 | Protocol Amendment: New and updated Investigator(s) - DORI-05, DORI-06, DORI-07, DORI-08, DORI-09, and DORI-10 |
| 3/04/05 | 106 | Protocol Amendment: Change in Protocol - DORI-05, Amendment 3 |
| 3/10/2005 | 107 | Safety Report: Follow-Up |
| 3/11/2005 | 108 | Safety Report: Follow-Up |
| 3/21/2005 | 109 | Protocol Amendment: Updated Investigator |
| 3/21/2005 | 110 | Information Amendment - Pharmacology/Toxicology |
| 3/28/2005 | 111 | Safety Report: Follow-Up |
| 3/31/2005 | 112 | Protocol Amendment: New Investigator(s) - DORI-05, DORI-06, DORI-07, DORI-08, DORI-09, and DORI-10 |
| 4/11/2005 | 113 | Information Amendment - CMC |
| 4/12/2005 | 114 | Safety Report: Follow-Up |
| 4/12/2005 | 115 | Safety Report: Follow-Up |
| 4/13/2005 | 116 | Safety Report: Follow-Up |
| 4/20/2005 | 117 | Information Amendment - Clinical |
| 4/22/2005 | 118 | Protocol Amendment: New Investigator(s) - DORI-06, DORI-08, DORI-09, and DORI-10 |
| 05/04/05 | 119 | Protocol Amendment: Change in Protocol - DORI-05, Amendment 4 and DORI-06, Amendment 3 |
| 5/6/2005 | 120 | Safety Report: Follow-Up |
| 5/12/2005 | 121 | Safety Report: Follow-Up |
| 5/23/2005 | 122 | Protocol Amendment: New Investigator(s) - DORI-05, DORI-06, DORI-07, DORI-09, and DORI-10 |
| 6/14/2005 | 123 | Information Amendment - Clinical |
| 06/21/05 | 124 | Safety Report: Follow-Up |
| 6/23/2005 | 125 | Information Amendment - Clinical |
| 6/23/2005 | 126 | Protocol Amendment: New Investigator(s) - DORI-06, DORI-08, DORI-09, and DORI-10 |
| 6/23/2005 | 127 | Information Amendment -Clinical |
| 6/30/2005 | 128 | Protocol Amendment: New Investigator(s) - DORI-05, DORI-06, DORI-07, DORI-08, DORI-09, and DORI-10 |
| 6/30/2005 | 129 | Safety Report: Follow-Up |
| 6/30/2005 | 130 | General Correspondence |
| 7/12/2005 | 131 | General Correspondence |

*Duplicate IND serial number inadvertently submitted.

| Date | Serial Number | Submission |
|---|---|---|
| 7/15/2005 | 132 | Safety Report: Follow-Up |
| 7/21/2005 | 133 | Safety Report: Initial |
| 8/11/2005 | 134 | Safety Report: Initial |
| 8/23/2005 | n/a | FDA Correspondence |
| 10/3/2005 | 135 | General Correspondence |
| 10/12/2005 | 135* | Safety Report: Follow-Up |
| 10/5/2005 | 136 | Protocol Amendment: Draft Phase I protocol |
| 10/28/2005 | 136* | Safety Report: Follow-Up |
| 10/7/2005 | 137 | Protocol Amendment: New Investigators; Updated Investigator Information - DORI-05, DORI-07, DORI-08, DORI-09, and DORI-10 |
| 10/28/2005 | 137* | Safety Report: Follow-Up |
| 10/18/2005 | 138 | Protocol Amendment: New Investigators; Updated Investigator Information - DORI-06, DORI-07, DORI-08, DORI-09, and DORI-10 |
| 10/28/2005 | 138* | Safety Report: Follow-Up |
| 10/18/2005 | 139 | Information Amendment - CMC |
| 11/2/2005 | 139* | Safety Report: Initial |
| 10/19/2005 | 140 | General Correspondence |
| 11/2/2005 | 140* | Safety Report: Initial |
| 10/20/2005 | 141 | Protocol Amendment: Change in Protocol - DORI-05, Amendment 5; DORI-06, Amendment 4; DORI-07, Amendment 3; DORI-08, Amendment 4 |
| 11/9/2005 | 141* | Safety Report: Initial |
| 10/25/2005 | 142 | Response to FDA Request For Information |
| 11/9/2005 | 142* | Safety Report: Initial |
| 10/26/2005 | 143 | General Correspondence: Type A Meeting Request |
| 11/15/2005 | 143* | Safety Report: Follow-Up |
| 10/28/2005 | 144 | General Correspondence |
| 11/15/2005 | 144* | Safety Report: Initial |
| 11/10/2005 | n/a | FDA Correspondence |
| 11/11/2005 | 145 | Protocol Amendment: New Investigators; Updated Investigator Information - DORI-08 and DORI-10 |
| 11/16/2005 | 146 | General Correspondence |
| 11/17/2005 | n/a | FDA Correspondence |
| 11/18/2005 | 147 | Safety Report: Follow-Up |
| 11/18/2005 | 148 | Safety Report: Follow-Up |
| 11/29/2005 | 149 | Protocol Amendment: DORI-07, Amendment 2 |
| 11/30/2005 | 150 | General Correspondence |
| 11/30/2005 | 151 | General Correspondence: |
| 12/2/2005 | 152 | Information Amendment - CMC |
| 12/13/2005 | 153 | Safety Report: Follow-Up |
| 12/19/2005 | 154 | General Correspondence: Type C Meeting Request |
| 12/20/2005 | 155 | General Correspondence |
| 12/21/2005 | 156 | Protocol Amendment: New Investigators; Updated Investigator Information - DORI-05, DORI-08 and DORI-10 |

*Duplicate IND serial number inadvertently submitted.

| Date | Serial Number | Submission |
|---|---|---|
| 12/22/2005 | 157 | General Correspondence: Type C Meeting Request |
| 12/27/2005 | 158 | Protocol Amendment: Submitted original protocol DORI-10-PK and Amendment 1 |
| 12/28/2005 | 159 | Safety Report: Initial |
| 1/3/2006 | n/a | FDA Correspondence |
| 1/4/2006 | n/a | FDA Correspondence |
| 1/4/2006 | 160 | Safety Report: Initial |
| 1/5/2006 | n/a | FDA Correspondence |
| 1/6/2006 | n/a | FDA Correspondence |
| 1/9/2006 | 161 | Safety Report: Initial |
| 1/11/2006 | 162 | General Correspondence |
| 1/11/2006 | n/a | FDA Correspondence |
| 1/12/2006 | 163 | General Correspondence |
| 1/13/2006 | 164 | Safety Report: Follow-Up |
| 1/13/2006 | 165 | General Correspondence |
| 1/18/2006 | 166 | Protocol Amendment: Submitted DORI-NOS-1001 PK Study Protocol. |
| 1/19/2006 | 167 | Safety Report: Follow-Up |
| 1/19/2006 | 168 | Safety Report: Follow-Up |
| 1/20/2006 | 169 | Protocol Amendment: Submitted new and updated investigator information for studies DORI-07, DORI-08, DORI-09, and DORI-10 |
| 1/23/2006 | 170 | Safety Report: Initial |
| 1/24/2006 | 171 | Protocol Amendment: DORI-09, Amendment 2 |
| 1/26/2006 | n/a | FDA Correspondence |
| 1/27/2006 | 172 | General Correspondence |
| 1/31/2006 | n/a | FDA Correspondence |
| 2/1/2006 | 173 | Safety Report: Follow-Up |
| 2/1/2006 | 174 | Safety Report: Follow-Up |
| 2/1/2006 | 175 | Annual Report: December 2, 2004-December 1, 2005) |
| 2/2/2006 | 176 | Safety Report: Follow-Up |
| 2/3/2006 | 177 | General Correspondence |
| 2/8/2006 | 178 | Safety Report: Follow-Up |
| 2/9/2006 | 179 | Safety Report: Initial |
| 2/9/2006 | 180 | Safety Report: Initial |
| 2/15/2006 | 181 | Safety Report: Initial |
| 2/16/2006 | 182 | Response to FDA Request For Information |
| 2/16/2006 | 183 | Safety Report: Follow-Up |
| 2/23/2006 | n/a | FDA Correspondence |
| 2/23/2006 | n/a | FDA Correspondence |
| 2/24/2006 | 184 | Safety Report: Initial |
| 2/27/2006 | 185 | Safety Report: Initial |
| 3/1/2006 | 186 | Safety Report: Follow-Up |
| 3/3/2006 | n/a | FDA Correspondence |
| 3/3/2006 | n/a | FDA Correspondence |

*Duplicate IND serial number inadvertently submitted.

| Date | Serial Number | Submission |
|---|---|---|
| 3/7/2006 | 187* | Safety Report: Initial |
| 3/7/2006 | 188 | Safety Report: Follow-Up |
| 3/9/2006 | 189 | Protocol Amendment: New Investigators/Updated Investigator Information - DORI-06, DORI-07, DORI-08, DORI-09, DORI-10, and DORI-NOS-1001 |
| 3/9/2006 | n/a | Record of Contact |
| 3/13/2006 | 190 | Safety Report: Follow-Up |
| 3/15/2006 | 191 | Information Amendment - CMC |
| 3/16/2006 | n/a | FDA Correspondence |
| 3/16/2006 | 192 | General Correspondence |
| 3/21/2006 | 193 | Safety Report: Initial |
| 3/21/2006 | 194 | Protocol Amendment: New Protocol, New Investigator - DORI-NOS-1004 |
| 3/21/2006 | 195 | Response to FDA Request for Information |
| 3/21/2006 | n/a | General Correspondence |
| 3/30/2006 | 196 | Safety Report: Follow-Up |
| 3/30/2006 | n/a | FDA Correspondence |
| 3/31/2006 | 197 | Protocol Amendment: DORI-NOS-1004, Amendment 1 |
| 4/4/2006 | n/a | FDA Correspondence |
| 4/5/2006 | n/a | FDA Correspondence |
| 4/7/2006 | 198 | Protocol Amendment: New Protocol; New Investigator - DORI-NOS-1006 |
| 4/7/2006 | 199 | Safety Report: Follow-Up |
| 4/7/2006 | n/a | FDA Correspondence |
| 4/13/2006 | 200 | Safety Report: Initial |
| 4/18/2006 | 201 | General Correspondence: Type B Meeting Request |
| 4/20/2006 | 202 | Protocol Amendment: New Investigators/Updated Investigator Information - DORI-08, DORI-09, and DORI-10. |
| 4/20/2006 | 203 | Safety Report: Initial |
| 4/21/2006 | 204 | Safety Report: Initial |
| 4/24/2006 | 205 | Protocol Amendment: Change in Protocol - DORI-09, Amendment 3 |
| 4/26/2006 | n/a | FDA Correspondence |
| 4/27/2006 | n/a | FDA Correspondence |
| 4/28/2006 | n/a | Record of Contact |
| 5/3/2006 | n/a | FDA Correspondence |
| 5/3/2006 | n/a | FDA Correspondence |
| 5/4/2006 | n/a | FDA Correspondence |
| 5/4/2006 | 206 | Protocol Amendment: New Protocol, New Investigator - DORI-NOS-1005 |
| 5/4/2006 | 207 | General Correspondence |
| 5/4/2006 | 208 | General Correspondence |
| 5/5/2006 | 209 | General Correspondence |
| 5/5/2006 | n/a | FDA Correspondence |

*Duplicate IND serial number inadvertently submitted.

| Date | Serial Number | Submission |
|---|---|---|
| 5/12/2006 | 210 | Safety Report: Initial |
| n/a | 211 | General Correspondence |
| 5/12/2006 | 212 | Safety Report: Follow-Up |
| 5/15/2006 | 213 | General Correspondence |
| 5/15/2006 | 214 | Protocol Amendment: Change in Protocol - DORI-10, Amendment 2 |
| 5/17/2006 | 215 | Safety Report: Initial |
| 5/17/2006 | 216 | Safety Report: Follow-Up |
| 5/18/2006 | 217 | General Correspondence |
| 5/18/2006 | 218 | Safety Report: Follow-Up |
| 5/19/2006 | n/a | FDA Correspondence |
| 5/23/2006 | 218 | Safety Report: Resubmitted Follow-Up |
| 5/23/2006 | 219 | General Correspondence |
| 5/23/2006 | 220 | Protocol Amendment: Change in Protocol, New Investigator, Updated Investigator Information - DORI-NOS-1005, Amendment 1; DORI-08, DORI-09, and DORI-10 new and updated investigator information |
| 5/24/2006 | 221 | Safety Report: Follow-Up |
| 5/25/2006 | 222 | Safety Report: Follow-Up |
| 5/25/2006 | 223 | General Correspondence |
| 5/26/2006 | 224 | Safety Report: Initial |
| 5/31/2006 | 225 | General Correspondence |
| 6/1/2006 | 226 | General Correspondence |
| 6/7/2006 | 227 | Response to FDA Request For Information |
| 6/8/2006 | n/a | FDA Correspondence |
| 6/9/2006 | 228 | Safety Report: Follow-Up |
| 6/20/2006 | 229 | Safety Report: Initial |
| 6/22/2006 | 230 | Safety Report: Follow-Up |
| 6/23/2006 | 231 | Protocol Amendment: DORI-NOS-1007 Study Protocol; new and updated investigator information for studies DORI-08, DORI-09, and DORI-10 |
| 6/23/2006 | 232 | General Correspondence |
| 6/23/2006 | 233 | Safety Report: Follow-Up |
| 6/26/2006 | n/a | FDA Correspondence |
| 6/28/2006 | 234 | Safety Report: Initial |
| 6/28/2006 | 235 | Safety Report: Initial |
| 6/29/2006 | 236 | Safety Report: Initial |
| 6/30/2006 | 237 | Safety Report: Follow-Up |
| n/a | 238 | General Correspondence |
| 7/12/2006 | n/a | FDA Correspondence |
| 7/13/2006 | 239 | Safety Report: Follow-Up |
| 7/14/2006 | 240 | Safety Report: Initial |
| 7/14/2006 | 241 | Safety Report: Follow-Up |
| 7/14/2006 | n/a | FDA Correspondence |
| 7/14/2006 | n/a | FDA Correspondence |
| 7/14/2006 | 242 | Safety Report: Follow-Up |

*Duplicate IND serial number inadvertently submitted.

| Date | Serial Number | Submission |
|---|---|---|
| 7/19/2006 | n/a | FDA Correspondence |
| 7/20/2006 | n/a | FDA Correspondence |
| 7/21/2006 | n/a | FDA Correspondence |
| 7/24/2006 | n/a | FDA Correspondence |
| 7/24/2006 | n/a | FDA Correspondence |
| 7/25/2006 | n/a | FDA Correspondence |
| 7/25/2006 | n/a | FDA Correspondence |
| 7/26/2006 | n/a | FDA Correspondence |
| 7/26/2006 | n/a | FDA Correspondence |
| 7/26/2006 | n/a | FDA Correspondence |
| 7/28/2006 | 243 | Protocol Amendment: Change in Protocol; New Investigator; Updated Investigator Information - DORI-NOS-1007, Amendment 1; new and updated investigator information for DORI-08, DORI-09, and DORI-10 |
| 7/31/2006 | n/a | FDA Correspondence |
| 7/31/2006 | n/a | FDA Correspondence |
| 8/1/2006 | n/a | FDA Correspondence |
| 8/2/2006 | 244 | Safety Report: Initial |
| 8/2/2006 | n/a | FDA Correspondence |
| 8/3/2006 | n/a | FDA Correspondence |
| 8/3/2006 | n/a | Record of Contact |
| 8/4/2006 | 245 | Safety Report: Initial |
| 8/4/2006 | n/a | FDA Correspondence |
| 8/4/2006 | n/a | FDA Correspondence |
| 8/7/2006 | 246 | Response to FDA Request For Information |
| 8/8/2006 | n/a | FDA Correspondence |
| 8/9/2006 | 247 | Response to FDA Request For Information |
| 8/10/2006 | n/a | FDA Correspondence |
| 8/14/2006 | 248 | Safety Report: Initial; Follow-Up 1 |
| 8/15/2006 | 249 | Safety Report: Follow-Up |
| 8/16/2006 | 250 | General Correspondence |
| 8/17/2006 | 251 | Safety Report (7-Day): Initial |
| 8/17/2006 | n/a | FDA Correspondence |
| 8/17/2006 | n/a | Record of Contact |
| 8/18/2006 | 252 | General Correspondence |
| 8/21/2006 | 253 | Safety Report: Follow-Up |
| 8/21/2006 | 254 | General Correspondence |
| 8/22/2006 | 255 | Safety Report: Follow-Up; Follow-Up |
| 8/24/2006 | n/a | FDA Correspondence |
| 8/25/2006 | n/a | FDA Correspondence |
| 8/29/2006 | 256 | Information Amendment - Clinical |
| 8/30/2006 | 257 | Information Amendment - Clinical |
| 8/30/2006 | 258 | Information Amendment - Clinical |
| 8/31/2006 | n/a | FDA Correspondence |
| 8/31/2006 | n/a | FDA Correspondence |

*Duplicate IND serial number inadvertently submitted.

| Date | Serial Number | Submission |
|---|---|---|
| 9/1/2006 | 259 | Safety Report (7-Day): Initial |
| 9/5/2006 | 260 | Safety Report: Initial |
| 9/5/2006 | n/a | FDA Correspondence |
| 9/7/2006 | 261 | Protocol Amendment: New Investigator; Updated Investigator Documentation - DORI-08, DORI-09, and DORI-10 |
| 9/14/2006 | 262 | Safety Report: Follow-Up |
| 9/14/2006 | n/a | FDA Correspondence |
| 9/19/2006 | 263 | Safety Report: Follow-Up |
| 9/21/2006 | n/a | FDA Correspondence |
| 9/22/2006 | 264 | General Correspondence |
| 9/22/2006 | 265 | General Correspondence |
| 9/22/2006 | n/a | FDA Correspondence |
| 9/25/2006 | 266 | Safety Report: Follow-Up |
| 9/25/2006 | 267 | Safety Report: Initial |
| 9/26/2006 | 268 | Safety Report (7-Day): Follow-Up |
| 9/27/2007 | n/a | FDA Correspondence |
| 9/27/2007 | n/a | FDA Correspondence |
| 9/29/2007 | 269 | Safety Report Follow-Up |
| 10/4/2006 | n/a | FDA Correspondence |
| 10/4/2006 | 270 | Safety Report: Initial |
| 10/4/2006 | n/a | FDA Correspondence |
| 10/4/2006 | n/a | FDA Correspondence |
| 10/5/2006 | 271 | General Correspondence |
| 10/5/2006 | 272 | General Correspondence |
| 10/6/2006 | n/a | FDA Correspondence |
| 10/6/2006 | n/a | FDA Correspondence |
| 10/9/2006 | 273 | Safety Report: Follow-Up |
| 10/10/2006 | 274 | Safety Report: Follow-Up |
| 10/12/2006 | 275 | Safety Report: Follow-Up |
| 10/12/2006 | n/a | FDA Correspondence |
| 10/13/2006 | n/a | FDA Correspondence |
| 10/18/2006 | 276 | Safety Report: Follow-Up |
| 10/19/2006 | 277 | Safety Report: Follow-Up |
| 10/24/2006 | 278 | Safety Report: Follow-Up |
| 10/26/2006 | n/a | FDA Correspondence |
| 10/26/2006 | n/a | FDA Correspondence |
| 10/26/2006 | 279 | General Correspondence |
| 10/27/2006 | n/a | FDA Correspondence |
| 10/31/2006 | n/a | FDA Correspondence |
| 10/31/2006 | n/a | FDA Correspondence |
| 11/2/2006 | n/a | FDA Correspondence |
| 11/2/2006 | 280 | Safety Report: Initial |
| 11/7/2006 | 281 | General Correspondence |
| 11/8/2006 | 282 | Safety Report: Follow-Up |
| 11/10/2006 | n/a | FDA Correspondence |

*Duplicate IND serial number inadvertently submitted.

| Date | Serial Number | Submission |
|---|---|---|
| 11/10/2006 | 283 | Response to FDA's Request For Information |
| 11/10/2006 | 284 | Safety Report: Follow-Up |
| 11/13/2006 | n/a | FDA Correspondence |
| 11/13/2006 | n/a | FDA Correspondence |
| 11/14/2006 | 285 | General Correspondence |
| 11/14/2006 | n/a | FDA Correspondence |
| 11/14/2006 | n/a | FDA Correspondence |
| 11/16/2006 | 286 | Safety Report: Initial |
| 11/16/2006 | 287 | General Correspondence: Type A Meeting Request |
| 11/16/2006 | n/a | Record of Contact |
| 11/21/2006 | n/a | FDA Correspondence |
| 11/22/2006 | 288 | Response to FDA Request For Information |
| 11/27/2006 | 289 | Safety Report: Follow-Up |
| 11/28/2006 | 290 | Safety Report: Follow-Up 2; Follow-Up |
| 11/28/2006 | n/a | FDA Correspondence |
| 11/30/2006 | 291 | Other: Submitted a petition to add a new term to the VA/Kaiser Permanente dictionary |
| 11/30/2006 | n/a | FDA Correspondence |
| 11/30/2006 | n/a | FDA Correspondence |
| 12/1/2006 | 292 | Protocol Amendment: New Investigator; Updated Investigator Documentation - DORI-05, DORI-07, DORI-09, and DORI-10 |
| 12/4/2006 | n/a | FDA Correspondence |
| 12/5/2006 | n/a | FDA Correspondence |
| 12/8/2006 | n/a | FDA Correspondence |
| 12/11/2006 | n/a | FDA Correspondence |
| 12/11/2006 | 293 | Safety Report: Initial; Follow-Up |
| 12/15/2006 | 294 | General Correspondence |
| 12/18/2006 | 295 | Safety Report: Follow-Up |
| 12/22/2006 | 296 | Safety Report: Initial |
| 12/28/2006 | 297 | Information Amendment -Preclinical |
| 12/28/2006 | n/a | FDA Correspondence |
| 1/2/2007 | 298 | Safety Report: Initial Safety; Follow-Up |
| 1/5/2007 | 299 | General Correspondence: Type C Meeting Request |
| 1/10/2007 | 300 | Safety Report: Initial; Initial; Follow-Up |
| 1/17/2007 | n/a | FDA Correspondence |
| 1/17/2007 | 301 | General Correspondence |
| 1/19/2007 | 302 | General Correspondence |
| 1/19/2007 | 303 | General Correspondence |
| 1/19/2007 | 304 | Safety Report: Follow-Up |
| 1/19/2007 | n/a | FDA Correspondence |
| 1/23/2007 | n/a | FDA Correspondence |
| 1/29/2007 | n/a | FDA Correspondence |
| 1/31/2007 | 305 | General Correspondence |

*Duplicate IND serial number inadvertently submitted.

| Date | Serial Number | Submission |
|---|---|---|
| 1/31/2007 | 306 | Protocol Amendment: New Investigator; Updated Investigator Documentation - DORI-05, DORI-06, DORI-07, DORI-08, DORI-09, DORI-010 |
| 1/31/2007 | n/a | FDA Correspondence |
| 2/1/2007 | 307 | General Correspondence |
| 2/1/2007 | n/a | Record of Contact |
| 2/5/2007 | 308 | Safety Report: Follow-Up |
| 2/6/2007 | 309 | Annual Report: Reporting Period: 12/2/05 - 12/1/06 |
| 2/8/2007 | 310 | Safety Report: Initial |
| 2/9/2007 | 311 | Safety Report: Follow-Up |
| 2/9/2007 | 312 | General Correspondence |
| 2/12/2007 | 313 | Response to FDA Request For Information |
| 2/12/2007 | 314 | Information Amendment: Clinical |
| 2/13/2007 | n/a | FDA Correspondence |
| 2/13/2007 | n/a | FDA Correspondence |
| 2/14/2007 | n/a | FDA Correspondence |
| 2/21/2007 | 315 | Safety Report: Follow-Up |
| 2/21/2007 | n/a | FDA Correspondence |
| 2/22/2007 | n/a | FDA Correspondence |
| 2/22/2007 | 316 | General Correspondence |
| 2/28/2007 | 317 | Information Amendment: Pharmacology/Toxicology |
| 3/6/2007 | n/a | FDA Correspondence |
| 3/8/2007 | n/a | FDA Correspondence |
| 3/9/2007 | n/a | FDA Correspondence |
| 3/15/2007 | 318 | Information Amendment: Pharmacology/Toxicology |
| 3/16/2007 | n/a | FDA Correspondence |
| 3/22/2007 | n/a | FDA Correspondence |
| 3/27/2007 | 319 | Safety Report: Initial |
| 3/28/2007 | n/a | FDA Correspondence |
| 3/28/2007 | n/a | FDA Correspondence |
| 3/29/2007 | n/a | FDA Correspondence |
| 4/3/2007 | 320 | Safety Report: Initial |
| 4/3/2007 | n/a | Record of Contact |
| 4/4/2007 | n/a | FDA Correspondence |
| 4/4/2007 | 321 | General Correspondence |
| 4/6/2007 | n/a | FDA Correspondence |
| 4/9/2007 | 322 | Safety Report: Initial |
| 4/12/2007 | 323 | Safety Report: Initial |
| 4/12/2007 | 323 | Safety Report: Initial |
| 4/13/2007 | 324 | Response to FDA Request For Information |
| 4/17/2007 | 325 | Safety Report: Follow-Up |
| 4/20/2007 | 326 | Information Amendment: Clinical |
| 4/24/2007 | 327 | Safety Report: Follow-Up |
| 4/24/2007 | 328 | Safety Report: Initial |
| 4/24/2007 | 328 | Safety Report: Initial |
| 4/30/2007 | 329 | Safety Report: Follow-Up; Follow-Up |

*Duplicate IND serial number inadvertently submitted.

| Date | Serial Number | Submission |
|---|---|---|
| 5/4/2007 | 330 | Information Amendment: CMC |
| 5/7/2007 | 331 | Protocol Amendment: New Protocol, New Investigator - DORI-NOS-1008 |
| 5/9/2007 | n/a | FDA Correspondence |
| 5/15/2007 | 332 | Protocol Amendment: New Investigator; Updated Investigator Documentation - DORI-09 and DORI-10 |
| 5/25/2007 | 333 | General Correspondence: Type C Meeting Request |
| 5/30/2007 | 334 | General Correspondence |
| 5/31/2007 | n/a | FDA Correspondence |
| 6/1/2007 | n/a | FDA Correspondence |
| 6/1/2007 | n/a | FDA Correspondence |
| 6/4/2007 | 335 | Safety Report: Follow-Up |
| 6/4/2007 | n/a | Safety Report: Initial |
| 6/4/2007 | 336 | Safety Report: Initial |
| 6/7/2007 | 337 | Safety Report: Follow-Up |
| 6/11/2007 | n/a | Record of Contact |
| 6/12/2007 | 338 | Response to FDA Request For Information: |
| 6/12/2007 | n/a | FDA Correspondence |
| 6/15/2007 | n/a | Safety Report: Initial |
| 6/15/2007 | 339 | Safety Report: Initial |
| 6/20/2007 | n/a | Safety Report: Initial |
| 6/20/2007 | 340 | Safety Report: Initial |
| 6/21/2007 | n/a | FDA Correspondence |
| 6/26/2007 | 341 | Protocol Amendment: New Investigator - DORINOS1008 and DORIINI2002 |
| 6/27/2007 | n/a | FDA Correspondence |
| 6/28/2007 | 342 | Safety Report: Follow-Up |
| 7/2/2007 | 343 | Safety Report: Initial; Initial |
| 7/5/2007 | 344 | Protocol Amendment: New Protocol, New Investigator |
| 7/5/2007 | 344 | Information Amendment: CMC |
| 7/6/2007 | 345 | Safety Report: Initial; Follow-Up ; Follow-Up |
| 7/9/2007 | n/a | FDA Correspondence |
| 7/9/2007 | n/a | Safety Report: Initial |
| 7/9/2007 | 346 | Safety Report: Initial |
| 7/9/2007 | 347 | Safety Report: Follow-Up; Follow-Up |
| 7/16/2007 | n/a | Safety Report: Initial |
| 7/16/2007 | 348 | Safety Report: Initial |
| 7/16/2007 | 349 | Safety Report: Initial |
| 7/19/2007 | n/a | FDA Correspondence: Follow-Up |
| 7/19/2007 | 350 | Safety Report: Follow-Up |
| 7/19/2007 | n/a | Safety Report: Initial |
| 7/19/2007 | 351 | Safety Report: Initial |
| 7/20/2007 | 352 | Information Amendment: Clinical - DORI-09 and Dori-10 |
| 7/20/2007 | n/a | Safety Report: Initial |
| 7/20/2007 | 353 | Safety Report: Initial |

*Duplicate IND serial number inadvertently submitted.

| Date | Serial Number | Submission |
|---|---|---|
| 7/24/2007 | 354 | General Correspondence |
| 7/27/2007 | 355 | Safety Report: Follow-Up |
| 8/7/2007 | 356 | Response to FDA Request For Information |
| 8/8/2007 | 357 | Safety Report: Follow-Up |
| 8/10/2007 | 358 | Protocol Amendment: New Investigator; Updated Investigator Information - DORINOS1008 and DORIINI2002 |
| 8/13/2007 | n/a | FDA Correspondence |
| 8/14/2007 | n/a | FDA Correspondence |
| 8/22/2007 | n/a | FDA Correspondence |
| 8/22/2007 | n/a | FDA Correspondence |
| 8/27/2007 | 359 | General Correspondence |
| 8/29/2007 | 360 | Safety Report: Follow-Up |
| 8/31/2007 | n/a | FDA Correspondence |
| 9/10/2007 | 361 | Protocol Amendment: New Investigator - DORINOS1008, DORINOS2001, and DORIINI2002 |
| 9/11/2007 | 362 | Safety Report: Initial |
| 9/17/2007 | 363 | Safety Report: Follow-Up |
| 9/18/2007 | 364 | Safety Report: Initial, Follow-Up |
| 9/19/2007 | 365 | Safety Report: Initial |
| 9/20/2007 | n/a | FDA Correspondence |
| 9/24/2007 | 366 | Safety Report: Initial, Initial, Follow-Up |
| 9/26/2007 | 367 | Safety Report: Follow-Up, Follow-Up, Follow-Up |
| 9/27/2007 | n/a | FDA Correspondence |
| 9/28/2007 | n/a | FDA Correspondence |
| 10/2/2007 | 368 | Safety Report: Follow-Up |
| 10/2/2007 | n/a | FDA Correspondence |
| 10/8/2007 | 369 | Safety Report: Initial, Initial, Follow-Up, Follow-Up |
| 10/10/2007 | 370 | Protocol Amendment: New Investigator; Updated Investigator Documentation - DORINOS1008, DORINOS2001, and DORIINI2002 |
| 10/12/2007 | 371 | Safety Report: Follow-Up, Follow-Up |
| 11/1/2007 | 372 | Protocol Amendment: New Protocol; New Investigator - DORI-NOS-1011<br>Information Amendment: Chemistry, Manufacturing, and Controls |
| 11/2/2007 | 373 | Protocol Amendment: New Protocol; New Investigator; Postmarketing Study Commitment Protocol - DORI-NOS-1003 |
| 11/2/2007 | n/a | FDA Correspondence |
| 11/5/2007 | 374 | Protocol Amendment: New Protocol; New Investigator - DORI-NOS-1010 |
| 11/5/2007 | n/a | Record of Contact |
| 11/9/2007 | 375 | Protocol Amendment: Change in Protocol; New Investigator; Updated Investigator Information - DORINOS1008, DORINOS2001, DORIINI2002 |
| 11/14/2007 | 376 | Protocol Amendment: New Protocol; New Investigator - DORI-NOS-1009 |

*Duplicate IND serial number inadvertently submitted.

| Date | Serial Number | Submission |
|---|---|---|
| 11/29/2007 | 377 | Protocol Amendment: New Protocol; New Investigator - DORINOS3008<br>Information Amendment: Chemistry, Manufacturing, and Controls |

## NDA 22-106 (Doripenem) US Submission Log

| Date | Submission |
|---|---|
| 11/28/2006 | General Correspondence: Drug User Fee Number: PD3006841 |
| 12/12/2006 | New Drug Application: Original NDA |
| 12/13/2006 | General Correspondence |
| 1/8/2007 | FDA Correspondence |
| 1/23/2007 | FDA Correspondence |
| 1/23/2007 | FDA Correspondence |
| 1/24/2007 | FDA Correspondence |
| 1/30/2007 | New Drug Application: Amendment 0001 |
| 2/5/2007 | FDA Correspondence |
| 2/21/2007 | FDA Correspondence |
| 2/22/2007 | FDA Correspondence |
| 2/22/2007 | FDA Correspondence |
| 2/23/2007 | FDA Correspondence |
| 2/23/2007 | FDA Correspondence |
| 2/26/2007 | FDA Correspondence |
| 2/28/2007 | FDA Correspondence |
| 2/28/2007 | FDA Correspondence |
| 3/16/2007 | FDA Correspondence |
| 3/21/2007 | FDA Correspondence |
| 3/30/2007 | New Drug Application: Amendment 0002 |
| 4/9/2007 | New Drug Application: Amendment 0004 |
| 4/11/2007 | New Drug Application: Amendment 0005 |
| 4/12/2007 | FDA Correspondence |
| 4/12/2007 | General Correspondence: Amendment 0003 |
| 4/12/2007 | New Drug Application: Amendment 0006 |
| 4/26/2007 | FDA Correspondence |
| 5/2/2007 | FDA Correspondence |
| 5/2/2007 | FDA Correspondence |
| 5/9/2007 | FDA Correspondence |
| 5/17/2007 | New Drug Application: Amendment 0007 |
| 5/18/2007 | New Drug Application: Amendment 0008 |
| 5/21/2007 | FDA Correspondence |
| 5/24/2007 | FDA Correspondence |
| 5/29/2007 | FDA Correspondence |
| 5/30/2007 | New Drug Application: Amendment 0009 |
| 5/30/2007 | FDA Correspondence |
| 5/31/2007 | FDA Correspondence |

*Duplicate IND serial number inadvertently submitted.

| Date | Submission |
|---|---|
| 5/31/2007 | FDA Correspondence |
| 6/1/2007 | FDA Correspondence |
| 6/4/2007 | New Drug Application: Amendment 0010 |
| 6/6/2007 | New Drug Application: Amendment 0011 |
| 6/14/2007 | FDA Correspondence |
| 6/14/2007 | FDA Correspondence |
| 6/14/2007 | FDA Correspondence |
| 6/14/2007 | Record of Contact |
| 6/15/2007 | FDA Correspondence |
| 6/15/2007 | FDA Correspondence |
| 6/15/2007 | FDA Correspondence |
| 6/20/2007 | FDA Correspondence |
| 6/20/2007 | Record of Contact |
| 6/22/2007 | New Drug Application: Amendment 0012 |
| 6/27/2007 | FDA Correspondence |
| 6/28/2007 | FDA Correspondence |
| 7/2/2007 | FDA Correspondence |
| 7/3/2007 | FDA Correspondence |
| 7/3/2007 | New Drug Application: Amendment 0013 |
| 7/9/2007 | FDA Correspondence |
| 7/10/2007 | FDA Correspondence |
| 7/12/2007 | New Drug Application: Amendment 0014 |
| 7/17/2007 | FDA Correspondence |
| 7/17/2007 | FDA Correspondence |
| 7/17/2007 | FDA Correspondence |
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| 7/17/2007 | FDA Correspondence |
| 7/20/2007 | FDA Correspondence |
| 7/23/2007 | FDA Correspondence |
| 7/24/2007 | FDA Correspondence |
| 7/24/2007 | FDA Correspondence |
| 7/25/2007 | FDA Correspondence |
| 7/26/2007 | FDA Correspondence |
| 7/26/2007 | FDA Correspondence |
| 7/26/2007 | General Correspondence: Amendment 0015 |
| 7/26/2007 | FDA Correspondence |
| 7/26/2007 | FDA Correspondence |
| 7/27/2007 | New Drug Application: Amendment 0016 |
| 7/30/2007 | FDA Correspondence |
| 7/31/2007 | FDA Correspondence |
| 8/1/2007 | FDA Correspondence |
| 8/2/2007 | FDA Correspondence |
| 8/2/2007 | Record of Contact |
| 8/2/2007 | Record of Contact |
| 8/3/2007 | FDA Correspondence |

*Duplicate IND serial number inadvertently submitted.

| Date | Submission |
|---|---|
| 8/3/2007 | FDA Correspondence |
| 8/3/2007 | FDA Correspondence |
| 8/6/2007 | FDA Correspondence |
| 8/6/2007 | Record of Contact |
| 8/7/2007 | FDA Correspondence |
| 8/7/2007 | FDA Correspondence |
| 8/7/2007 | Record of Contact |
| 8/8/2007 | FDA Correspondence |
| 8/8/2007 | FDA Correspondence |
| 8/9/2007 | FDA Correspondence |
| 8/9/2007 | New Drug Application: Amendment 0017 |
| 8/9/2007 | General Correspondence |
| 8/9/2007 | FDA Correspondence |
| 8/9/2007 | FDA Correspondence |
| 8/10/2007 | FDA Correspondence |
| 8/10/2007 | FDA Correspondence |
| 8/10/2007 | New Drug Application: Amendment 0018 |
| 8/10/2007 | New Drug Application: Amendment 0019 |
| 8/13/2007 | FDA Correspondence |
| 8/14/2007 | FDA Correspondence |
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| 8/15/2007 | FDA Correspondence |
| 8/17/2007 | FDA Correspondence |
| 8/17/2007 | FDA Correspondence |
| 8/17/2007 | FDA Correspondence |
| 8/17/2007 | FDA Correspondence |
| 8/17/2007 | New Drug Application: Amendment 0020 |
| 8/17/2007 | New Drug Application: Amendment 0021 |
| 8/17/2007 | Response to FDA Request For Information: Amendment 0022 |
| 8/21/2007 | FDA Correspondence |
| 8/21/2007 | FDA Correspondence |
| 8/21/2007 | General Correspondence |
| 8/21/2007 | FDA Correspondence |
| 8/24/2007 | New Drug Application: Amendment 0023 |
| 8/24/2007 | New Drug Application: Amendment 0024 |
| 8/24/2007 | FDA Correspondence |
| 8/24/2007 | FDA Correspondence |
| 8/27/2007 | FDA Correspondence |
| 8/28/2007 | FDA Correspondence |
| 8/28/2007 | FDA Correspondence |
| 8/28/2007 | FDA Correspondence |
| 8/28/2007 | New Drug Application: Amendment 0025 |
| 8/30/2007 | FDA Correspondence |
| 8/30/2007 | FDA Correspondence |
| 8/30/2007 | FDA Correspondence |

*Duplicate IND serial number inadvertently submitted.

| Date | Submission |
|---|---|
| 8/31/2007 | FDA Correspondence |
| 9/3/2007 | FDA Correspondence |
| 9/4/2007 | Response to FDA Request For Information: NDA Amendment 0026 |
| 9/4/2007 | Response to FDA Request For Information: NDA Amendment 0027 |
| 9/4/2007 | Response to FDA Request For Information: NDA Amendment 0028 |
| 9/4/2007 | Response to FDA Request For Information: NDA Amendment 0029 |
| 9/4/2007 | FDA Correspondence |
| 9/4/2007 | FDA Correspondence |
| 9/4/2007 | FDA Correspondence |
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| 9/4/2007 | FDA Correspondence |
| 9/7/2007 | FDA Correspondence |
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| 9/11/2007 | FDA Correspondence |
| 9/11/2007 | FDA Correspondence |
| 9/12/2007 | FDA Correspondence |
| 9/12/2007 | General Correspondence: NDA Amendment 0030 |
| 9/13/2007 | FDA Correspondence |
| 9/13/2007 | Response to FDA Request For Information: NDA Amendment 0031 |
| 9/13/2007 | FDA Correspondence |
| 9/13/2007 | FDA Correspondence |
| 9/14/2007 | FDA Correspondence |
| 9/14/2007 | FDA Correspondence |
| 9/17/2007 | FDA Correspondence |
| 9/18/2007 | Response to FDA Request For Information: NDA Amendment 0032 |
| 9/18/2007 | FDA Correspondence |
| 9/20/2007 | FDA Correspondence |
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| 9/26/2007 | FDA Correspondence |
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| 9/27/2007 | FDA Correspondence |

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| Date | Submission |
|---|---|
| 9/27/2007 | FDA Correspondence |
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| 9/27/2007 | FDA Correspondence |
| 9/27/2007 | FDA Correspondence |
| 9/28/2007 | FDA Correspondence |
| 10/1/2007 | FDA Correspondence |
| 10/2/2007 | FDA Correspondence |
| 10/2/2007 | Response to FDA Request For Information: NDA Amendment 0033 |
| 10/2/2007 | FDA Correspondence |
| 10/2/2007 | FDA Correspondence |
| 10/2/2007 | FDA Correspondence |
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| 10/3/2007 | FDA Correspondence |
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| 10/5/2007 | FDA Correspondence |
| 10/5/2007 | FDA Correspondence |
| 10/5/2007 | FDA Correspondence |
| 10/8/2007 | Response to FDA Request For Information: NDA Amendment 0034 |
| 10/8/2007 | FDA Correspondence |
| 10/8/2007 | FDA Correspondence |
| 10/9/2007 | FDA Correspondence |
| 10/9/2007 | FDA Correspondence |
| 10/9/2007 | FDA Correspondence |
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| 10/10/2007 | FDA Correspondence |
| 10/10/2007 | FDA Correspondence |
| 10/11/2007 | FDA Correspondence |
| 10/11/2007 | FDA Correspondence |
| 10/11/2007 | Response to FDA Request For Information: NDA Amendment 0035 |
| 10/12/2007 | FDA Correspondence |
| 10/12/2007 | FDA Correspondence |
| 10/12/2007 | FDA Correspondence |
| 10/12/2007 | FDA Correspondence |
| 10/12/2007 | FDA Correspondence |
| 10/12/2007 | FDA Correspondence |
| 10/12/2007 | FDA Correspondence |
| 10/12/2007 | FDA Correspondence |

*Duplicate IND serial number inadvertently submitted.

| Date | Submission |
|---|---|
| 10/15/2007 | Advertising |
| 10/17/2007 | Advertising |
| 10/19/2007 | Advertising |
| 10/23/2007 | FDA Correspondence |
| 10/24/2007 | Advertising |
| 10/25/2007 | General Correspondence: NDA Amendment 0036 |
| 10/26/2007 | Advertising |
| 10/26/2007 | General Correspondence |
| 10/26/2007 | Advertising |
| 10/31/2007 | General Correspondence: NDA Amendment 0037 |
| 11/2/2007 | Advertising |
| 11/2/2007 | FDA Correspondence |
| 11/5/2007 | Advertising |
| 11/19/2007 | Advertising |
| 11/20/2007 | Advertising |
| 11/21/2007 | Advertising |
| 11/21/2007 | Advertising |
| 11/27/2007 | Advertising |
| 11/27/2007 | Advertising |

## NDA 22-171 (Doripenem) US Submission Log

| Date | Submission |
|---|---|
| 6/5/2007 | New Drug Application: Review Aid - PK Data (Desk Copy) |
| 6/5/2007 | New Drug Application: Original NDA |
| 6/20/2007 | FDA Correspondence |
| 6/27/2007 | FDA Correspondence |
| 6/28/2007 | FDA Correspondence |
| 6/28/2007 | FDA Correspondence |
| 7/3/2007 | New Drug Application: Amendment 0001 |
| 7/9/2007 | FDA Correspondence |
| 7/17/2007 | FDA Correspondence |
| 7/17/2007 | FDA Correspondence |
| 7/17/2007 | FDA Correspondence |
| 7/20/2007 | FDA Correspondence |
| 7/23/2007 | FDA Correspondence |
| 7/23/2007 | FDA Correspondence |
| 7/25/2007 | FDA Correspondence |
| 7/26/2007 | FDA Correspondence |
| 7/26/2007 | General Correspondence: Amendment 0002 |
| 7/26/2007 | FDA Correspondence |
| 7/26/2007 | FDA Correspondence |
| 7/26/2007 | FDA Correspondence |
| 7/26/2007 | FDA Correspondence |

*Duplicate IND serial number inadvertently submitted.

| Date | Submission |
|---|---|
| 7/30/2007 | FDA Correspondence |
| 7/31/2007 | FDA Correspondence |
| 8/1/2007 | FDA Correspondence |
| 8/1/2007 | FDA Correspondence |
| 8/2/2007 | Record of Contact |
| 8/2/2007 | Record of Contact |
| 8/2/2007 | FDA Correspondence |
| 8/3/2007 | FDA Correspondence |
| 8/3/2007 | FDA Correspondence |
| 8/3/2007 | FDA Correspondence |
| 8/6/2007 | FDA Correspondence |
| 8/6/2007 | Record of Contact |
| 8/7/2007 | FDA Correspondence |
| 8/7/2007 | FDA Correspondence |
| 8/7/2007 | Record of Contact |
| 8/8/2007 | FDA Correspondence |
| 8/8/2007 | FDA Correspondence |
| 8/9/2007 | FDA Correspondence |
| 8/10/2007 | FDA Correspondence |
| 8/10/2007 | New Drug Application: Response to FDA Request For Information: Amendment 0003 |
| 8/10/2007 | New Drug Application: Response to FDA Request For Information: Amendment 0004 |
| 8/13/2007 | FDA Correspondence |
| 8/14/2007 | FDA Correspondence |
| 8/15/2007 | FDA Correspondence |
| 8/17/2007 | FDA Correspondence |
| 8/17/2007 | FDA Correspondence |
| 8/17/2007 | FDA Correspondence |
| 8/28/2007 | FDA Correspondence |
| 8/30/2007 | FDA Correspondence |
| 9/4/2007 | Response to FDA Request For Information: NDA Amendment 0005 |
| 9/4/2007 | FDA Correspondence |
| 9/6/2007 | Record of Contact |
| 9/7/2007 | FDA Correspondence |
| 9/7/2007 | FDA Correspondence |
| 9/7/2007 | FDA Correspondence |
| 9/10/2007 | Response to FDA Request For Information: NDA Amendment 0006 |
| 9/10/2007 | FDA Correspondence |
| 9/17/2007 | FDA Correspondence |
| 10/1/2007 | Safety Update: NDA Amendment 0007 |
| 10/2/2007 | FDA Correspondence |
| 10/23/2007 | FDA Correspondence |
| 11/2/2007 | FDA Correspondence |
| 11/5/2007 | Record of Contact |
| 11/6/2007 | FDA Correspondence |

*Duplicate IND serial number inadvertently submitted.

| Date | Submission |
|---|---|
| 11/7/2007 | FDA Correspondence |
| 11/8/2007 | FDA Correspondence |
| 11/12/2007 | Response to FDA Request For Information: NDA Amendment 0008 |
| 11/19/2007 | FDA Correspondence |
| 11/20/2007 | FDA Correspondence |
| 11/20/2007 | Response to FDA Request For Information: NDA Amendment 0009 |

*Duplicate IND serial number inadvertently submitted.

**Exhibit 6**

**Power of Attorney Appointing Thomas J. Dodd**
**As Representative of the Owner of the '016 Patent**

Exhibit 1 *Power of Attorney*

# *IN THE UNITED STATES PATENT AND TRADEMARK OFFICE*

**Patent No.:** 5,317,016 **Issued: May 31, 1994**
**Expiration Date: August 14, 2012**

**Inventors:** Yasuhiro Nishitani; Tadashi Irie; Yutaka Nishino

**Title:** Pyrrolidylthiocarbapenem Derivative

## Limited Power of Attorney

The undersigned, who is empowered to sign this certificate on behalf of the assignee, hereby appoints the following practitioners for the limited purpose of filing and prosecuting an extension of US Patent No. 5,317,016 pursuant to 35 U.S.C. §156(d) and 37 C.F.R. §1.740:

Philip Johnson, Esq. (Registration No. 27,200)
Thomas J. Dodd, Esq. (Registration No. 31,010)
Bernard F. Plantz, Esq. (Registration No. 32,091)
Mary A. Appollina, Esq. (Registration No. 34,087)
John W. Harbour, Esq. (Registration No. 31,365)
Hal B. Woodrow, Esq. (Registration No. 32,501)

Johnson & Johnson
One Johnson Drive
New Brunswick, NJ 08933
Phone: (732) 524-2782
Facsimile: (732) 524-2808

## Certification Under 37 C.F.R. §3.73(b)

Shionogi Seiyaku Kabushiki Kaisha, A Japanese corporation, certifies that it is the assignee of the entire right, title and interest in the patent application identified above by virtue of either:

☒ A chain of title from the inventor(s), or the patent application identified above, to the current assignee as shown below:

From: Inventors: Yasuhiro Nishitani; Tadashi Irie; Yutaka Nishino

To: Shionogi Seiyaku Kabushiki Kaisha

The document was recorded in the Patent and Trademark Office at Reel 006224 Frame 0329, or for which a copy thereof is attached.

☒ Copies of assignments or other documents in the chain of title are attached.

The undersigned has reviewed all the documents in the chain of title of the patent application identified above, and to the best of the undersigned's knowledge and belief, title is in the assignee identified above.

**The undersigned (whose title is supplied below) is empowered to sign this certificate on behalf of the assignee.**

**I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements and the like so made, are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.**

September 25, 2007
**Date**

Motozo Shiono
**Signature**

Motozo SHIONO
**Typed or Printed Name**

President
**Title**

Shionogi Seiyaku Kabushiki Kaisha
**Company**

YAMA-113

ASSIGNMENT

WHEREAS: The ASSIGNOR, comprising the following named inventor(s)

1. Yasuhiro NISHITANI; 49-16, Aoba-dai, Izumi-shi, Osaka Japan

2. Tadashi IRIE; 1-1-C-13-201, Momoyama-dai, Suita-shi, Osaka Japan

3. Yutaka NISHINO; 5-2, Nakakamida-cho, Neyagawa-shi, Osaka Japan

has invented and owns a certain invention entitled:

A PYRROLIDYLTHIOCARBAPENEM DERIVATIVE

for which application for Letters Patent of the United States was executed on even date herewith, and

WHEREAS, the ASSIGNEE

SHIONOGI SEIYAKU KABUSHIKI KAISHA
3-1-8, Dosho-machi, Chuo-ku, Osaka-shi, Osaka Japan

is desirous of acquiring the entire interest in, to and under said invention and the United States Letters Patent to be obtained therefor;

NOW, THEREFORE, TO ALL WHOM IT MAY CONCERN: Be it known that in consideration of the payment by ASSIGNEE to ASSIGNOR of the sum corresponding to One Dollar ($1.00), the receipt of which is hereby acknowledged, and for other good and valuable consideration, ASSIGNOR hereby sells, assigns and transfers to ASSIGNEE the full and exclusive right, title and interest to said invention and all Letters Patent of the United States to be obtained therefor on said application or any

continuation, division, renewal, substitute or reissue thereof for the full term or terms for which the same may be granted.

ASSIGNOR hereby covenants that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment and sale;

ASSIGNOR further covenants that ASSIGNEE will, upon its request, be provided promptly with all pertinent facts and documents relating to said application, said invention and said Letters Patent as may be known and accessible to ASSIGNOR and will testify as to the same in any interference or litigation related thereto and will promptly execute and deliver to ASSIGNEE or its legal representative any and all papers, instruments or affidavits required to apply for, obtain, maintain and enforce said application, said invention and said Letters Patent which may be necessary or desirable to carry out the purposes hereof.

IN WITNESS WHEREOF, have hereunto set hand and seal this 10th day of August , 1992.

1. Yasuhiro Nishitani
(Yasuhiro NISHITANI)

2. Tadashi Irie
(Tadashi IRIE)

3. Yutaka Nishino
(Yutaka NISHINO)

**Exhibit 7**

**STATEMENT THAT APPLICANT IS ELIGIBLE**
**FOR EXTENSION AND LENGTH OF EXTENSION CLAIMED**

***IN THE UNITED STATES PATENT AND TRADEMARK OFFICE***

Patent No.: 5,317,016

Issued: May 31, 1994
Expiration Date: August 14, 2012

Inventors: Yasuhiro Nishitani; Tadashi Irie; Yutaka Nishino

Title: PYRROLIDYLTHIOCARBAPENEM DERIVATIVE

**Statement of Eligibility for Extension of**
**Patent Term Due to Regulatory Review**

I, Thomas J. Dodd, represent that I am the attorney of record duly appointed by the assignee of the entire right, title and interest in the patent application identified above, and do state on behalf of the Applicant as follows:

To the best of my knowledge, U.S. Patent No. 5,317,016 (the '016 Patent) meets all of the eligibility criteria set forth in 37 C.F.R §§1.710 and 1.720 for extension of patent term.

The '016 Patent claims a "product" as that term is defined in 37 C.F.R §1.710, specifically the active ingredient, doripenem (present in the form of doripenem monohydrate), its composition and use, of a new human drug, DORIBAX™ (Doripenem) 37 C.F.R §1.720(a).

The term of the '016 Patent has never been previously extended. 37 C.F.R §1.720(b).

An application for extension of the term of the '016 Patent in compliance with 37 C.F.R §1.740 is herewith submitted. 37 C.F.R §1.720(c).

The approved product, DORIBAX™ (Doripenem), has been subject to a regulatory review period before its commercial marketing or use as defined in 35 U.S.C. §156(g). 37 C.F.R §1.720(d).

The approved product, DORIBAX™ (Doripenem), has received permission for commercial marketing or use and the permission for the commercial marketing or use of the product is the first received permission for commercial marketing or use under the provision of law under which the applicable regulatory review occurred. 37 C.F.R §1.720(e).

The application for extension of the term of the '016 Patent submitted herewith is submitted within the sixty-day period beginning on the date the product first received permission for commercial marketing or use under the provisions of law under which the applicable regulatory review period occurred. 37 C.F.R §1.720(f).

The term of the '016 Patent, including any interim extension issued pursuant to § 1.790, has not expired before the submission of an application in compliance with 37 C.F.R. § 1.741. 37 C.F.R §1.720(g).

No other patent term has been extended for the same regulatory review period for the approved product, DORIBAX™ (Doripenem), 37 C.F.R §1.720(h).

The extension claimed is 1025 days, setting the patent to expire on June 5, 2015. The following are the calculations, made in accordance with 37 C.F.R. § 1.775, that result in the claimed extension:

(1) The testing phase began on January 2, 2003 (the effective date of the IND) and ended on December 12, 2006 (submission date of the NDA).

(2) The approval phase began on December 12, 2006 (day of receipt by the FDA of the NDA) and approval was granted on October 12, 2007.

(3) The total number of days in the testing phase (from and including January 2, 2003 to and including December 11, 2006) is 1441 days from the start date to the end date, end date included. One half of the testing phase is 721 days.

(4) The total number of days in the approval phase is (from and including December 12, 2006 to and including October 12, 2007) is 304 days from the start date to the end date, end date included.

(5) The patent issued on May 31, 1994, before the regulatory approval process began.

(6) Applicant acted with due diligence throughout the entire regulatory review period.

(7) The sum of the (a) number of days in one half of the testing phase (721), and (b) number of days in the approval phase (304) is: 1025

(8) The original expiration date of the patent is August 14, 2012.

(9) Addition of the extension of 1025 days to the original expiration date of the patent extends the expiration date of the patent to June 5, 2015.

(10) Fourteen years from the approval date of the product (October 12, 2007) is October 12, 2021.

(11) Pursuant to 35 U.S.C. §156(c)(3), the extended term of the patent cannot exceed 14 years from the date of product approval. The fourteen year cap does not apply since the extension of 1025 days sets the patent to expire on June 5, 2015, which is before the date that is 14 years post-approval (October 12, 2021).

(12) Pursuant to 35 U.S.C. §156(g)(6)(A), the extension period is subject to a five year limitation (for patents issued after September 24, 1984). The five year limitation does not apply since the extension of 1025 days patent is less than five years.

(13) In light of the conclusions set forth above, the extended expiration date of the '016 Patent is believed to be June 5, 2015.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment,

or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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